ABSTRACTS OF WORLD MEDICINE

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Pathology

EXPERIMENTAL PATHOLOGY

1. **The Influence of Hyaluronic Acid and Other Substances on Tensile Strength of Healing Wounds**
H. PINKUS and E. T. PERRY. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **21**, 365–374, Dec., 1953. 5 figs., 13 refs.

In a study carried out at the Detroit Institute of Cancer Research and Wayne University College of Medicine, Detroit, bilateral skin incisions, 2·5 cm. long and extending down to the muscle, were made parallel to the spine in the trunk of young adult guinea-pigs. Saline solutions of hyaluronic acid (40 mg. per 100 ml.) were injected directly into the wound on one side (0·2 ml. twice a week) or indirectly through an indwelling polythene tube (0·1 ml. four times a week), while similar injections of hyaluronidase (150 turbidity reducing units per ml. of saline) were made into the wound on the other side. The animals were killed at intervals of 5 to 7 days, and the tensile strength of the wound estimated by determining the pressure of air required to rupture the wound, an excised disk of wound-bearing skin being used as a drum-head.

From their findings the authors conclude that in wounds less than 7 weeks old, those injected with hyaluronidase have a greater tensile strength than those injected with hyaluronic acid, but that after 7 weeks this relationship is reversed.

[The method of estimating the tensile strength—similar to that used by Blank (*J. invest. Derm.*, 1952, **18**, 433)—is ingenious and neat; but, as the authors admit, their results are too fragmentary to warrant definite conclusions.] *A. Wynn Williams*

2. **Dynamics of Inflammation and of Repair. IV. Chemotactic Substances in Normal Tissues**
V. H. MOON, C. G. GRAND, and G. A. TERSHAKOVEC. *Archives of Pathology* [*Arch. Path.* (*Chicago*)] **57**, 44–50, Jan., 1954. 4 figs., 11 refs.

At the University and the Cancer Institute of Miami, Florida, the authors carried out tests for the presence of chemotactic substances in extracts and fragments of various normal tissues (from rabbits, rats, and 14-day-old chick embryos) which had been allowed to undergo autolysis for 2 to 3 hours and had then been freeze-dried. The tests were performed with leucocytes obtained from the buffy coat of blood or from the splenic tissue of chick embryos by three different methods: (1) a microcapillary-tube technique; (2) implantation of tissue fragments in tissue-culture medium 0·5 mm. from an explant of clotted buffy coat or splenic tissue containing leucocytes; and (3) the slide-and-coverslip method of McCutcheon. By the first two methods, although there were some differences in the results obtained with leucocytes from blood and splenic tissue, positive evidence was obtained of the presence of a chemotactic substance in normal liver, lung, spleen, skin, and testis, whereas normal brain, kidney, and muscle showed no chemotactic properties; bruised muscle, however, was strongly chemotactic. By the third method variation in the activity of the leucocytes was observed from test to test and from day to day with the same materials, the reaction being positive on one occasion and negative on the next; this may be explained on the basis of the suggestion of Ketchel and Favour (*Science*, 1953, **118**, 79) that there is some factor in the plasma of different individuals which causes marked variations in the migratory activity of leucocytes *in vitro*.

The demonstration *in vitro* that normal tissues contain chemotactic substances gives additional support to the hypothesis that the release of such substances from damaged tissues provides the trigger mechanism which initiates the processes of acute inflammation.

A. Ackroyd

3. **The Mechanism of Alloxan Protection in Experimental Atherosclerosis**
D. L. COOK, L. M. MILLS, and D. M. GREEN. *Journal of Experimental Medicine* [*J. exp. Med.*] **99**, 119–124, Feb. 1, 1954. 1 fig., 15 refs.

Experiments are described in which 3 groups of rabbits, after a control period on normal diet, were given a diet containing 1% cholesterol for 56 days. Group I consisted of 5 animals rendered diabetic with alloxan. Group II consisted of 7 animals which had received a similar dose of alloxan but in which the arteries of the pancreas were clamped for 5 minutes after the injection, the alloxan thus being prevented from producing diabetes. Group III contained 10 normal control animals. The food consumption, weight, serum lipoprotein (S_f 5 to 9 and 16 to 30) and cholesterol levels, and blood glucose content of all the animals were determined regularly during the experiment, after which they were killed and the aorta examined. The total surface area of atherosclerotic intima was measured, and the average serum lipoprotein and cholesterol levels during the test period calculated for each animal and for each group. Animals in Group I consumed about twice as much food

as those in Groups II and III, and their serum cholesterol and lipoprotein levels were significantly higher. However, the degree of atherosclerosis found in the three groups did not differ significantly.

These results show that the exaggerated hypercholesterolaemia and lipoproteinaemia of animals treated with alloxan is due to increased food intake as a result of the animals' diabetic state, and confirm that the atherogenic mechanism usually associated with hypercholesterolaemia was retarded in Group I. The fact that the animals in Group II developed the same degree of atherosclerosis as those in Group I despite a lesser food intake suggests that the protective effect of alloxan is associated with its diabetogenic action on the pancreas. *Peter Harvey*

4. Effect of Diets on the Anemia, Azotemia, and Survival of Bilaterally Nephrectomized Rabbits

H. CLARK, P. GRAHAM, and E. E. MUIRHEAD. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **43**, 113–118, Jan., 1954. 11 refs.

The influence of various diets on the blood volume and haematocrit value and on the uraemia of nephrectomized rabbits was studied at the University of Texas, Dallas. Bilateral nephrectomy was carried out on 50 rabbits, which were then divided into five equal groups and fed as follows: Group 1, high-protein and high-carbohydrate diet; Group 2, water only; Group 3, fat–sugar emulsion; Group 4, low-glucose diet; and Group 5, high-glucose diet. Two groups of intact rabbits were fed on a fat–sugar emulsion and a normal diet respectively.

The diets were given to the nephrectomized animals as suspensions or solutions by gastric intubation to a total of 7 ml. per kg. body weight per day. All the rabbits except those given a normal diet lost weight. Anaemia was marked in the rabbits in Group 3 and mild in Group 1; Groups 2, 4, and 5 had moderate anaemia. The blood urea level rose at comparable rates in Groups 1, 3, and 4, and rather more rapidly in Group 2; the rise was slowest in Group 5. Mild anaemia was noted in the intact animals, but no change was observed in the blood urea level. The average survival time of the nephrectomized rabbits was: 3·8 days in Group 1, 5·1 days in Group 2, 5·2 days in Group 3, 7·1 days in Group 4, and 6·7 days in Group 5.

The authors conclude that a high-glucose diet is more protective in the nephrectomized rabbit than fasting or a diet of protein or fat with carbohydrate. The fat–sugar emulsion did not cause diarrhoea. *K. G. Lowe*

5. The Natural History of Experimental Glomerulonephritis Produced by Foreign Protein

J. D. HAMILTON and N. E. FREMES. *American Journal of Pathology* [*Amer. J. Path.*] **30**, 127–145, Jan.–Feb., 1954. 16 figs., 15 refs.

Working at Toronto University, the authors have studied the renal lesions developing in 6 rabbits following reversed passive anaphylaxis to horse serum. They found slight generalized changes, some of which were recognizable in one animal that died after only 40 minutes. In other experiments, 45 rabbits were given two injections of horse serum at 10-day intervals 3 weeks after unilateral nephrectomy. Animals were killed and examined at intervals for 32 weeks, during which the transformation of proliferative to degenerative changes, with development of hyalinization, was observed. Of these 45 rabbits, 30 developed arteritis and 28 nephritis, but there was no constant relationship between these two types of hypersensitivity reaction. *J. B. Enticknap*

6. Studies in Fibrosis of the Liver Induced by Carbon Tetrachloride. I. Relation between Hepatocellular Injury and New Formation of Fibrous Tissue. II. A Quantitative Study of the Effect of Cortisone on Fibrosis of the Liver in Rats. III. Pantothenic Acid and Liver Fibrosis

K. ATERMAN. *Archives of Pathology* [*Arch. Path.* (*Chicago*)] **57**, 1–29, Jan., 1954. 20 figs., bibliography.

There is a lack of agreement in the literature about the distribution of fibrous tissue in the liver of the experimental animal after prolonged treatment with carbon tetrachloride (CCl_4). The present author, working at the University of Birmingham, therefore undertook a series of investigations into the relation between hepatocellular injury and the new formation of fibrous tissue in rats. Carbon tetrachloride was injected subcutaneously twice weekly in doses of 0·1 to 0·2 ml., 21 to 63 injections being given and the animals killed and examined at various intervals, thus enabling the development of fibrosis to be followed through its various stages. The first changes in the liver become apparent within a few hours of the first injection of CCl_4 and consist of hydropic degeneration of the liver cells either immediately beneath the capsule or surrounding the central hepatic vein. The cells surrounding the portal tract remain intact. After a varying interval, depending on the susceptibility of the animal to CCl_4, delicate fibrous bands gradually appear amongst these hydropic cells. These fibrous bands slowly thicken and show a tendency to connect branches of the hepatic veins, thus producing a pseudo-lobular pattern with disorganization of the normal lobular pattern. Gradually the cellular changes and subsequent fibrous-band proliferation extend to include the portal vessels. Only when the fibrosis is well advanced is there a fall in numbers, and ultimately disappearance, of the hydropic cells. In a second experiment two groups of rats receiving CCl_4 were given 7·125 mg. of cortisone daily for 10 days, between the 26th and 29th injections and between the 60th and the 63rd injections of CCl_4 respectively, and were then killed after having received 71·25 mg. of cortisone. The collagen content of the liver of these animals, estimated by Neuman and Logan's method, was compared with that of animals receiving CCl_4 alone for the same periods. In the animals killed after 14 weeks' CCl_4 (early fibrotic stage) cortisone treatment significantly reduced the amount of collagen present and increased the fat content of the liver, but in the animals killed after 31 weeks' CCl_4 (late fibrotic stage) it had no effect on the amount of collagen or fat in the liver, and a high mortality rate resulted. Estimates of the degree of fibrosis of the liver made from histological sections stained by the silver impregnation method for

reticulum correlated better with estimates of the collagen content determined chemically than did those from sections stained with Mallory's azocarmine stain. The author suggests that the change from the early, reversible, fibrosis of the liver to the late, irreversible, stage may result from alterations in adrenal function.

In a third experiment the livers of rats given an excess of calcium pantothenate throughout the period of administration of CCl_4 showed no significant differences either in their histology or in their collagen content from those of animals receiving CCl_4 alone.

A. Ackroyd

7. Nature of Liver Failure due to Complete Biliary Obstruction

C. A. MACGREGOR. *Archives of Surgery* [*Arch. Surg. (Chicago)*] **67**, 878–901, Dec., 1953. 7 figs., bibliography.

Although changes in liver function in obstructive jaundice have often been described, it is not easy in clinical practice to distinguish between the effects of uncomplicated biliary obstruction and those of infection or liver-cell damage. The author, at Harvard Medical School, Boston, studied the effect of complete uncomplicated biliary obstruction in 6 dogs by carrying out serial liver function tests from the time the common bile duct was divided until death. There was a progressive fall in the serum albumin level with a rise in α- and β-globulin values. The response to the intravenous galactose tolerance test was normal. There was an abrupt rise after operation in the serum levels of cholesterol, alkaline phosphatase, and bilirubin, after which these values decreased gradually. The plasma prothrombin concentration fell progressively, but death occurred before haemorrhagic levels were attained. Although calorie intake was usually adequate until the terminal stages, there was continuous loss of weight with disappearance of subcutaneous fat and emaciation.

P. C. Reynell

8. Further Studies of Hepatic Structure and Function by Fluorescence Microscopy

A. L. GRAFFLIN and E. G. CORDDRY. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] **93**, 205–224, Oct., 1953. 1 fig., 27 refs.

In an attempt to elucidate the mechanism of biliary excretion, the authors have carried out experiments at the Johns Hopkins University School of Medicine in which mice, rats, and frogs were given non-toxic doses of fluorescent dyes and the surface of the liver of the anaesthetized or freshly killed animal studied by fluorescence microscopy. Full experimental details were given in a previous paper (Grafflin and Bagley, *Bull. Johns Hopk. Hosp.*, 1952, **90**, 395). In the present paper they provide some technical data on fluorescence emission spectra and give a detailed description of the abnormalities developing in bile canaliculi and liver cells under various conditions, such as more or less prolonged observation, ultraviolet irradiation, and cauterization. The bile canaliculi showed "beading" (that is, irregular discontinuous delineation of the canaliculi by fluorescein without apparent change in calibre), a more extensive form of discontinuity of delineation, the formation of fine intracellular "tendrils", and "sprouting" into intracellular vacuoles. The liver cells showed vacuolation, abnormally increased fluorescence, and turbidity of the cytoplasm.

The significance of these findings is discussed rather inconclusively, the authors seeming to imply that they represent a common pattern of reaction of the liver to various injuries.

[It is unfortunate that the authors have been unable to illustrate this, or previous papers on the same subject, with fluorescence photomicrographs of the appearances described, preferring to refer the reader to illustrations in papers by other workers. The abstracter can endorse their commendation of the monograph by Hanzon on this method of studying liver function (*Acta. Physiol. Scand.*, 1952, **28**, Suppl. 101) as a more comprehensive work, more relevant to current problems in pathology and physiology, and illustrated by many excellent photomicrographs.] *M. C. Berenbaum*

9. Experimental Studies on the Colloid-chemical Mechanism of Gall-stone Formation. [In English]

J. KLEEBERG. *Gastroenterologia* [*Gastroenterologia (Basel)*] **80**, 313–339, Dec., 1953. 10 figs., bibliography.

At the Rothschild–Hadassah University Hospital, Jerusalem, the author studied the part played by "colloid-chemical forces" in the formation of gall-stones. By means of an ingenious physico-chemical model of gelatin, silver nitrate, and silver dichromate, he was able to produce *in vitro*: (1) periodic precipitations; (2) large single concretions which he regarded as comparable to large solitary gall-stones; and (3) multiple polyhedric centres of precipitation within a gelatin matrix, which he considered to be similar to the multiple, faceted stones formed in gall-bladder disease. The results are discussed at length, and it is suggested that colloidal-osmotic factors play a much larger part in the formation of gall-stones than do pressure and simple dehydration.

Walter H. H. Merivale

10. The Action of Cortisone on Transplanted and Induced Tumors in Mice

R. BASERGA and P. SHUBIK. *Cancer Research* [*Cancer Res.*] **14**, 12–16, Jan., 1954. 6 figs., 28 refs.

The action of cortisone has been studied on the heterologous transplantation, growth, and metastatic diffusion of a transplantable adenocarcinoma in DBA mice, and on the genesis, growth, and metastatic diffusion of tumors induced in the skin and subcutaneous tissues of Swiss mice with methylcholanthrene. Cortisone did not show any appreciable influence on the heterologous transplantation of a mammary adenocarcinoma from DBA mice and on the growth of methylcholanthrene-induced tumors in Swiss mice. The growth rate of a transplanted adenocarcinoma in DBA mice was temporarily inhibited by the administration of cortisone. The induction of skin tumors in Swiss mice by methylcholanthrene has been markedly inhibited by the administration of 0·5 mg. of cortisone daily. Cortisone has been found to favor an increased metastatic spread of all the experimental tumors studied.—[Authors' summary.]

11. Studies on the Pathogenesis of Kernicterus. With Special Reference to the Nature of Kernicteric Pigment and its Deposition under Natural and Experimental Conditions

F. S. VOGEL. *Journal of Experimental Medicine* [*J. exp. Med.*] **98**, 509–520, Nov. 1, 1953. 3 figs., 16 refs.

The pigment which stains the basal grey matter in kernicterus differs from bilirubin in that it has a canary colour and fades slowly on exposure to air or formalin, whereas bilirubin gives a darker stain and is converted to biliverdin on exposure.

In a study carried out at the New York Hospital–Cornell Medical Center, New York, the absorption spectrum of chloroform extracts of the brains of 3 infants with kernicterus was shown to be identical with that of mesobilirubin, a reduction product of bilirubin. The author also found that bilirubin injected into the brains of kittens was very quickly removed, whereas the injection of mesobilirubin resulted in local staining which persisted for at least 2 weeks.

Microscopically, mesobilirubin was found both inside and outside the nerve cells; in these experiments the cells themselves seemed to be unharmed by the pigment, and the author therefore suggests that the pigment is probably not responsible for the degenerative changes commonly found in cases of kernicterus. How the mesobilirubin is deposited is not known. It has been shown that brain tissue can reduce bilirubin, though slowly, and it is possible that the blood–brain barrier for bilirubin is altered when there is severe liver damage at birth; the bilirubin injected experimentally into the brains of newborn kittens was probably removed by the blood stream before it could be reduced to mesobilirubin. *J. Foley*

CHEMICAL PATHOLOGY

12. Postprandial Hypolipemia of Pancreatic Fibrocystic Disease. A Diagnostic Test

E. F. HIRSCH, L. CARBONARO, A. D. BIGGS, and F. L. PHILLIPS. *American Journal of Diseases of Children* [*Amer. J. Dis. Child.*] **86**, 721–725, Dec., 1953. 10 refs.

Perhaps the best method of establishing that the secretion of the pancreas is normal or abnormal is the estimation of the trypsin content of aspirated duodenal fluid. However, as this procedure presents certain difficulties, various indirect methods have been proposed. At the University of Chicago Medical School the authors studied the esterified fatty acid content of the blood in 3 groups of children before, and 3 to 4 and 6 hours after, the ingestion of 36% cream given in the fasting state in a dose of 4 g. per kg. body weight. The subjects were 11 normal infants and children aged 8 weeks to 7 years, 6 children with fibrocystic disease of the pancreas drawn from 3 families, and 4 children from the same families who were not suffering from the disease.

In the group of normal children the postprandial increase in serum fatty acid content ranged from 32 to 196%. In the 6 children with fibrocystic disease there was only a slight or no increase in these values postprandially (0 to 20·5%), in marked contrast to that in their brothers or sisters, who showed normal responses (86 to 211%). It is suggested that the response of the serum level of esterified fatty acids to a high-fat meal could be made the basis of a diagnostic test for fibrocystic disease of the pancreas.

Walter H. H. Merivale

13. A New Liver Function Turbidity Test

H. N. ANTONIADES. *Journal of Clinical Pathology* [*J. clin. Path.*] **6**, 290–293, Nov., 1953. 7 refs.

A new liver function test is described in which the reagent is diethylbarbituric acid (0·44 g. in 1 litre of water). To 4 ml. of this solution 0·05 ml. of fresh, unhaemolysed serum is added and the tube immersed in a boiling water-bath for 1 minute. The resulting turbidity is compared with the standard turbidity tubes used for the estimation of protein in urine, a turbidity equivalent to 50 mg. of protein per 100 ml. or more being indicative of liver disorder.

This test and the thymol test of Maclagan were carried out at the Evangelismos Hospital, Athens, on serum from a total of 1,692 subjects, including healthy persons and patients with various diseases, and the results compared. In 280 normal subjects, 811 cases of non-hepatic disease, and 246 cases of obstructive jaundice, cancer of the liver, or gall-bladder disease, the results of both tests were negative. The result of the diethylbarbituric acid test was positive in all of 218 cases of hepatic cirrhosis, infective hepatitis, or chronic obstruction of the bile ducts, whereas that of the thymol test was positive in only 176 of these; the former was positive in 30 out of 34 cases of enlarged liver associated with heart disease, and the latter in 27 cases; while of 4 cases with hepatosplenic disorders, the former was positive in one and the latter negative in all. The diethylbarbituric acid test also gave a positive reaction in all of 5 cases of subacute bacterial endocarditis, in all of 9 cases of syphilitic hepatitis, in 27 out of 30 cases of amoebiasis, and also in cases of kala-azar and leprosy.

Examination of 17 sera giving a positive response showed the globulin content in each case to be 2·9 g. per 100 ml. or more (normal range 1·5 to 3·0 g. per 100 ml.). The strength of the reaction increased with increasing globulin content of the serum.

M. Lubran

14. The Determination of Calcium in Biological Fluids by Flame Photometry

F. J. N. POWELL. *Journal of Clinical Pathology* [*J. clin. Path.*] **6**, 286–289, Nov., 1953. 18 refs.

The flame photometer cannot be used for the direct determination of calcium in blood and urine owing to interference by other ions. But if the calcium is first precipitated as the oxalate and the precipitate then dissolved in perchloric acid, the estimation can be carried out as accurately as in the case of sodium and potassium. Oxalate depresses the calcium readings considerably, but this effect is greatly reduced by the added perchloric acid. Results obtained by flame photometry are in very good agreement with those given by the customary permanganate titration method.

In practice, 2 ml. of serum and 3 ml. of oxalate buffer (10 ml. 0·1 M oxalic acid + 190 ml. 0·1 M ammonium oxalate) are mixed in a tube graduated at 4 ml., allowed to stand for 30 minutes, and centrifuged. The supernatant is discarded and 0·05 N perchloric acid added to the 4-ml. mark. The tube is then shaken well and the solution sprayed into the flame photometer. A solution of calcium chloride (5 mg. per 100 ml.) is used as a standard. For urine or other fluids the final solution is diluted, if necessary, to bring the calcium concentration to about 5 mg. per 100 ml. *M. Lubran*

HAEMATOLOGY

15. On the Optical Properties of the Hemoglobin in Microdrepanocytic Disease

A. ASCENZI and E. SILVESTRONI. *Blood* [*Blood*] **8**, 1061–1066, Dec., 1953. 2 figs., 28 refs.

Microdrepanocytic disease occurs in subjects who are heterozygous for both the drepanocytic (sickle-cell) and the microcythaemic (thalassaemic) traits, and is clinically almost identical with sickle-cell anaemia. The sickling of erythrocytes in the last-named disease appears to be associated with the presence of an abnormal type of haemoglobin (Type S) which can be identified by its property of birefringence. The authors here report observations made at the University of Rome on the optical properties of erythrocytes and haemoglobin solutions from patients with microdrepanocytic disease and from carriers of the sickle-cell trait.

When the blood of patients with the former disease was exposed to reduced oxygen pressure, some of the erythrocytes were found to undergo sickling while others did not although they might show micropoikilocytosis. On examination with the polarizing microscope only the sickled cells were birefringent, their optical axis being perpendicular to their length and the average retardation 7·5 to 0·15 mμ, whence it is estimated that the birefringence was of the order of 0·0037. Solutions of reduced haemoglobin obtained from patients with microdrepanocytic disease or from carriers of the sickle-cell trait were shown to form birefringent pseudocrystalline aggregates or tactoids, the shape and optical properties of which were closely similar to those of sickled cells. It is suggested, therefore, that the chemical basis of microdrepanocytic disease is identical with that of sickle-cell anaemia, and that " sickling is primarily due to a pseudocrystalline aggregation of reduced S hemoglobin ".

George Discombe

16. An Electron Microscope Study of Sectioned Cells of Peripheral Blood and Bone Marrow

J. KAUTZ and Q. B. DEMARSH. *Blood* [*Blood*] **9**, 24–38, Jan., 1954. 6 figs., bibliography.

This paper from the University of Washington School of Medicine, Seattle, gives a report of observations on the structure of leucocytes as revealed by electron microscopy of sectioned material. Unsectioned cells are too thick for penetration by the electron beam, while the possible presence of artefacts in preparations of cell components obtained by autolysis or other traumatic methods renders observations on such material of doubtful value. By centrifuging human blood, separating the buffy coat, mixing it with warm 10% gelatin in saline, and allowing it to gel, the authors were able to cut ultra-thin sections of normal blood cells 0·05 μ or less in thickness. [For details of the technique of handling and fixing, the reader should consult the original paper.] Electron micrographs were taken and enlarged photographically to give a final magnification of $\times$ 15,000, which permitted details of the structure of most of the usual types of leucocyte and their granules and mitochondria to be studied and described.

[Those interested should consult the original article, in which a number of the authors' excellent photomicrographs are reproduced. This new technique promises to be of considerable value in studies of the cyto-architecture of both normal and pathological blood cells.]

Nigel Compston

17. The Osmotic Properties of the Normal Human Erythrocyte

E. B. HENDRY. *Edinburgh Medical Journal* [*Edinb. med. J.*] **61**, 7–24, Jan., 1954. 14 refs.

At the Western Infirmary, Glasgow, the author has studied the effects of hypotonic solutions of various alkaline salts on human erythrocyte volume. The usual haematocrit method of determining cell volume is discussed, and criticized on the grounds that the use of the centrifuge at low speeds results in an appreciable amount of plasma being left in the erythrocyte layer, and at high speeds in some degree of compression of any swollen cells. It has also been shown that the results obtained by this method can be considerably altered at will by increasing the speed or prolonging the period of centrifugation.

In the method adopted by the author, based on that proposed by Stewart 55 years ago (*J. Physiol.*, 1899, **24**, 211), changes in cell volume are determined by measuring the change in total plasma protein concentration in the extracellular medium when sodium chloride and distilled water are added. The method has the great advantage that it does not involve high-speed centrifuging. The author claims that this method shows the normal human erythrocyte to act as a perfect osmometer.

Marjorie Le Vay

18. The Incidence and Significance of Iron-containing Granules in Human Erythrocytes and their Precursors

A. S. DOUGLAS and J. V. DACIE. *Journal of Clinical Pathology* [*J. clin. Path.*] **6**, 307–313, Nov., 1953. 4 figs., 19 refs.

The incidence and significance of siderocytes—erythrocytes in which iron-containing granules can be demonstrated—in the peripheral blood and bone marrow were studied by the authors at the Postgraduate Medical School of London. In order to demonstrate the granules, films of peripheral blood and marrow were fixed with methyl alcohol for 10 to 20 minutes, followed by treatment for 10 minutes in a water-bath at 56° C. with a fresh mixture of equal parts of 2% potassium

ferrocyanide and 2% hydrochloric acid. After washing in running water for 20 minutes and rinsing in a dilute buffer at *p*H 6·8, the films were counterstained with 0·1% safranin. This method was also applied to films which had been stained for reticulocytes with cresyl blue.

Siderocytes contain 1 to 12 or more granules—most commonly 1 or 2 situated near the periphery of the cell. Usually the size of the granules varies inversely with their number, the maximum diameter being about 2 μ. Cells containing Pappenheimer bodies are found as frequently as siderocytes in the peripheral blood. Few, if any, of the granules of diffuse punctate basophilia are iron-containing. Erythroblasts in the marrow or peripheral blood may contain iron granules, 1 to 10 or more in number; in pathological states they may be 2 to 3 μ in diameter. Iron granules are usually present in erythroblasts containing haemoglobin; in some diseases they may occur in early basophilic normoblasts. The granules are usually not seen in marrow films stained with Romanowsky dyes, the cytoplasm of erythroblasts containing the granules showing only a diffuse, uniform polychromasia.

The incidence of normoblasts with iron-containing granules in the bone marrow of 18 normal subjects was 24 to 81%, with a mean of 49%. In iron-deficiency anaemia the normoblasts were consistently free from iron granules, whereas in most other conditions the incidence of iron-containing granules in the normoblasts was within the normal range. When iron-deficient patients were treated with iron, the granules returned to the normoblasts of the marrow. Extracorpuscular haemosiderin was never present in the marrow in cases of iron deficiency in which there were no iron granules in the normoblasts, although iron granules might be present in normoblasts in the absence of extracorpuscular iron ; but if extracorpuscular iron was present, iron granules were always found in the normoblasts. The size of the granules did not increase when the marrow iron content was greatly increased by repeated transfusion. In 3 patients with a defect of haemoglobin synthesis the granules were abnormally large.

Siderocytes were absent from 19 normal subjects examined. Their incidence was low in most diseases, except in a few isolated cases. Splenectomy gave rise to an increase in siderocytes in the peripheral blood, irrespective of the nature of the primary condition, and an approximately equal increase in Pappenheimer bodies also occurred. In 11 cases with normal erythropoiesis, siderocytes formed up to 14% of the total count (mean 4%). In congenital and acquired haemolytic anaemias the number of siderocytes in the peripheral blood rose considerably after splenectomy. In hereditary spherocytosis the incidence of siderocytes was less and the granules were fewer and much smaller.

M. Lubran

19. **Platelet Antibody Tests in the Diagnosis of Purpura**
J. L. TULLIS. *New England Journal of Medicine* [*New Engl. J. Med.*] **249**, 591–595, Oct. 8, 1953. 14 refs.

Writing from the New England Deaconess Hospital (Harvard University), Boston, the author describes a simple test for platelet antibodies for use in the differentiation of different types of purpura. A mixture of preserved platelets, human complement, and the serum to be tested is incubated at 37° C. and studied for changes in the total platelet count at the end of 45 and 90 minutes, morphological changes or the presence of clumping being also recorded. The result is expressed simply as positive or negative, no attempt at gradation of severity being made. Full details of the method are given.

Of 26 patients with secondary thrombocytopenic purpura, 25 showed a fall of only 2 to 6% in the total number of platelets, these values being similar to those found in the serum of 104 normal control subjects. Of 18 cases of idiopathic thrombopenic purpura, however, in half, the test gave a positive result, indicating the presence of circulating antiplatelet antibody, the average fall in platelet count being 17% at 45 minutes and 24% at 90 minutes. The author suggests that the demonstration of the presence of antibodies by this method could be of value in the planning of therapy, by distinguishing those cases that will not respond to platelet transfusion.

Marjorie Le Vay

20. **The Finding of the L.E. (Lupus Erythematosus) Cells in Smears of Untreated, Freshly Drawn Peripheral Blood**
B. CHOMET, M. M. KIRSHEN, G. SCHAEFER, and P. MUDRIK. *Blood* [*Blood*] **8**, 1107–1109, Dec., 1953. 2 figs., 5 refs.

In this paper from the Mount Sinai Hospital, Chicago, the authors report the finding of a few typical L.E. cells in a direct smear of untreated peripheral blood from a patient dying from acute systemic lupus erythematosus. As the authors state, this finding was remarkable, because the formation of L.E. cells has hitherto been regarded as occurring only *in vitro*. There was no doubt about the diagnosis, which was confirmed at necropsy. It is suggested that the L.E. factor was probably present in the serum in high concentration, and that the time elapsing between the withdrawal of blood and the fixation of the smear may have been just sufficient to permit the formation of L.E. cells.

[The authors' suggestion that the appearance of L.E. cells in freshly-drawn blood in this case can still be considered a post-vital artefact is almost certainly correct, as current opinion favours the view that L.E. cells can never be produced *in vivo*.]

E. G. Rees

MORBID ANATOMY AND CYTOLOGY

21. **Pathology of Juvenile Nasopharyngeal Angiofibroma, a Lesion of Adolescent Males**
S. S. STERNBERG. *Cancer* [*Cancer* (*N.Y.*)] **7**, 15–28, Jan., 1954. 26 figs., 7 refs.

The author reports from the Memorial Center for Cancer and Allied Diseases, New York, the results of a study of the histological appearances in specimens from 25 cases of juvenile nasopharyngeal angiofibroma, many of which were previously described in a clinical study by Martin *et al.* (*Ann. Surg.*, 1948, **127**, 513; *Abstracts of*

World Surgery, 1948, **4**, 202). He shows in a series of fine photomicrographs the characteristic structural changes which take place in these uncommon benign (but expansile and infiltrating) tumours. The main clinical symptoms of the condition are nasal obstruction and attacks of epistaxis. All patients in this series were adolescent males. Linkage with sex and age is suspected, although this has not been definitely determined. Histogenetically, chiefly on the grounds of the finding of a common underlying basic vascular structure of the tumours—despite their variable histological pattern—the author believes that these tumours represent a special form of angioma. *L. Michaelis*

22. **Primary Cardiac Amyloidosis**
A. I. THOMASHOW, W. D. ANGLE, and T. G. MORRIONE. *American Heart Journal* [*Amer. Heart J.*] **46**, 895–905, Dec., 1953. 3 figs., 11 refs.

Two cases of amyloidosis limited to the heart and one of amyloidosis involving the heart and lungs are described in this paper from the Long Island College Hospital, New York. At necropsy on 3 elderly male patients amyloid deposits, unsuspected during life, were found in the heart and, in one of the patients, in the alveolar septa and small arteries of the lungs as well. The deposits, which were distributed throughout the whole of the myocardium, were small in one case and extensive in the others. In all cases the amyloid material gave a positive reaction to the Congo-red test and a negative reaction to iodine. In 2 cases a metachromatic staining reaction was obtained with crystal violet. One patient, aged 85, died from rupture of an aneurysm of the aortic arch; one, aged 89, from essential hypertension; and the third, aged 74, from pulmonary emphysema.

The classification of amyloidosis is briefly discussed, with special reference to primary amyloidosis affecting the heart of elderly subjects, for which King (*Amer. J. Path.*, 1948, **24**, 1095; *Abstracts of World Medicine*, 1949, **5**, 673) proposed the term " atypical amyloidosis associated with senility ". The authors emphasize the difficulty of reaching a diagnosis on clinical grounds in these cases.

[No reference is made to the possibility of syphilis in the patient who died from rupture of an aortic aneurysm, and this raises doubt about the " primary " nature of the amyloidosis. In one of the other cases tuberculous lesions were found in the lungs and mediastinal lymph nodes.] *A. Wynn Williams*

23. **The Changing Morphologic Picture of Endocarditis since the Advent of Chemotherapy and Antibiotic Agents**
A. ANGRIST and J. MARQUISS. *American Journal of Pathology* [*Amer. J. Path.*] **30**, 39–63, Jan.–Feb., 1954. 12 figs., 22 refs.

The authors have made a systematic study of the striking changes in the incidence and appearance of vegetations on the cardiac valves which have occurred since the advent of chemotherapy and antibiotics by comparing the findings in 5,033 necropsies performed at Queens General Hospital, Jamaica, New York, between 1936 and 1946 with those in 3,643 necropsies carried out after that time (1946–51). There were only 39 cases of acute rheumatic and 5 of atypical verrucous endocarditis in the whole series and these were not included in the study.

Before 1946 there were 93 cases of bacterial (1·85%) and 99 of non-bacterial endocarditis (1·97%). Since that year, 17 cases of bacterial (0·47%) and 163 of non-bacterial endocarditis (4·47%) have occurred. The increased incidence of " thrombotic non-bacterial endocardiosis " (as the authors call the non-specific non-bacterial disease) was largely in patients over 50 years of age (1·6% rising to 4·8%), whereas the decrease in the bacterial cases was mostly in those below the age of 50 (3·2 to 0·9%). About 23% of all cases of non-bacterial endocardiosis showed infarcts in the brain, kidney, spleen, heart, or extremities, and in about two-thirds of these cases there was no other obvious cause. The authors consider that transitional forms between the various types of endocarditis are becoming more common, and give a number of illustrative case histories in support of this view. *J. B. Enticknap*

24. **The Morphology of the " Vascular Spiders " in the Skin of Patients with Disease of the Liver.** (Zur Morphologie der Gefässspinnen (" vascular spiders ") in der Haut Leberkranker)
G. A. MARTINI and J. STAUBESAND. *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin* [*Virchows Arch. path. Anat.*] **324**, 147–164, 1953. 12 figs., 32 refs.

Recognition of the significance of " vascular spiders " is much more recent in Germany than in Great Britain. This paper from the Anatomical Institute, University of Hamburg, describes a purely anatomical approach to the problem of their nature, based on serial-section reconstructions of 18 biopsy specimens, 14 of which were from cases of liver disease, 2 from women in pregnancy, and 2 from apparently normal subjects.

The structure was found to be constant in all. A single relatively large artery (the " central spider artery ") runs up through the dermis to end in a sub-epidermal dilatation, the " spider-ampulla ". Initially this artery has a normal structure, but its muscular layer first becomes eccentric in distribution and then, with the elastic lamina, disappears altogether, so that the ampulla is sinus-like. From the ampulla radiates a series of small efferent branches, which have the histological structure of small veins but terminate in capillaries. The ampulla and its efferent branches together produce the naked-eye appearance of the " spider ". Despite the vein-like appearance of the efferent branches, no direct arterio-venous communication within the spiders was demonstrated in any of the specimens. However, independent but apparently related anastomoses were seen in several cases in the adjoining subcutis.

[This paper in general confirms the anatomical findings of Bean (*Medicine* (*Baltimore*), 1945, **24**, 243) but gives a considerably more detailed account. The absence of support for a glomus origin of the spiders, which some authors have suggested on rather inadequate evidence, is noteworthy.] *Bernard Lennox*

Bacteriology

VIRUSES

25. **Type C Influenza Virus. I. Studies of the Virus and its Distribution**
E. MINUSE, J. J. QUILLIGAN, and T. FRANCIS. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **43**, 31–42, Jan., 1954. 1 fig., 18 refs.

The viruses which cause epidemic influenza are divided into two types, A and B. From an outbreak of mild influenza occurring in 1950 a virus was isolated similar in many respects to Types A and B, but sufficiently distinctive to be named Type C. This paper gives a useful account of the properties of this virus as defined in the laboratory, and describes serological investigations carried out to determine the prevalence of antibodies to it.

The Type-C virus differs in some important respects from the other types of influenza virus, the more important being its failure to agglutinate guinea-pig erythrocytes, the increased haemagglutination titres obtained with fowl erythrocytes at $+6^{\circ}$ C., a variation in haemagglutination titres with erythrocytes from different human individuals (apparently unrelated to their blood group), and different absorption–elution characteristics with erythrocytes. The virus could not be adapted to mice, and was established with difficulty in ferrets and hamsters, in which the most consistent involvement was found in the turbinates. Studies of the haemagglutination–inhibition antibodies to the virus in human sera showed that the titre was high in most adults, whereas in children it was low. Paired sera from children among whom an epidemic of mild influenza had occurred showed a rise in antibody titre. Among adults, although widely sought, the virus has been isolated only from a few sporadic cases of mild, undifferentiated, upper respiratory illness.

J. E. M. Whitehead

26. **Type C Influenza Virus. II. Intranasal Inoculation of Human Individuals**
J. J. QUILLIGAN, E. MINUSE, and T. FRANCIS. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **43**, 43–47, Jan., 1954. 1 fig., 5 refs.

The experimental production of infection by influenza virus C in human adults was attempted by spraying 1 ml. of 12th-passage amniotic fluid into the nostrils of 6 women known to have low titres of haemagglutination-inhibiting antibodies to this virus. In a different room a control group of 5 women were inoculated similarly with normal allantoic fluid. For 16 days after inoculation the subjects were observed, but none developed any clinical sign or symptom of respiratory infection. The virus was isolated from the garglings of 5 of the 6 inoculated individuals up to 4 days after inoculation. In 4 of the 6 women a significant rise in antibody titre had occurred by the 14th day. Although none of the experimental subjects developed any clinical evidence of infection, the investigator who had carried out the inoculations, during which considerable coughing and sneezing had taken place, developed a moderately severe, but afebrile, coryza 7 days later. On the third day of his illness the virus was isolated from throat washings, and the antibody titre of his blood underwent a fourfold rise between the second and twelfth days after onset.

J. E. M. Whitehead

27. **Electron Microscopic Studies of Erythrocytes from a Patient with Infectious Mononucleosis**
R. L. REAGAN, E. D. PALMER, and A. L. BRUECKNER. *American Journal of Pathology* [*Amer. J. Path.*] **29**, 1161–1163, Nov.–Dec., 1953. 2 figs., 4 refs.

Electron microscopy of erythrocytes from a patient infected with infectious mononucleosis showed the virus-like particles to be spherical, with irregular contour. The virus-like particles have a diameter of 160 to 200 mμ. These bodies could not be demonstrated in normal human blood subjected to the same procedure of preparation and electron microscopic examination. These bodies resemble the virus of influenza described by Stanley and the virus of measles described by us.

The patient's serum contained heterophile antibodies and other signs were present that are considered diagnostic for infectious mononucleosis.—[Authors' summary.]

BACTERIA

28. **The Use of Metabolites in the Restoration of the Viability of Heat and Chemically Inactivated *Escherichia coli***
F. HEINMETS, W. W. TAYLOR, and J. J. LEHMAN. *Journal of Bacteriology* [*J. Bact.*] **67**, 5–12, Jan., 1954. 11 refs.

Experiments indicate that suspensions of *Escherichia coli*, strain B/r, which have been sterilized by the action of heat, chlorine, " zephiran " chloride, and ethyl alcohol contain viable cells when incubated with various metabolites of the tricarboxylic acid cycle. When such " sterile " suspensions are incubated in buffer or in nutrient broth, no viable cells can be demonstrated. In the present series, the following metabolites were most effective in producing reactivation. (1) Heat " killed ": sodium citrate, lactic acid, and oxalacetic acid; (2) chlorine " killed ": sodium citrate, malic acid, and oxalacetic acid; (3) hydrogen peroxide " killed ": sodium citrate, lactic acid, *cis*-aconitic acid; (4) zephiran chloride " killed ": sodium citrate, lactic acid, *cis*-aconitic acid, and *iso*citric acid; (5) ethyl alcohol " killed ": *cis*-aconitic acid, α-ketoglutaric acid, succinic acid, etc.; (6) the combination of 11 metabolites produced the highest reactivation.

Reactivation processes of bacterial cells are discussed in terms of resynthesis of enzymes and re-establishment of cyclic processes.

It is indicated that conventional testing and culturing methods are not adequate to determine the levels of " complete " sterility.—[Authors' summary.]

29. The Concentration, Microculture, and Sensitivity Testing of *M. tuberculosis*

H. M. RICE and F. C. ROWAN. *Journal of Clinical Pathology* [*J. clin. Path.*] **6**, 261–265, Nov., 1953. 3 figs., 4 refs.

The authors describe their experiences at Nottingham General Hospital with a microculture technique for *Mycobacterium tuberculosis* and their results from its application to sensitivity tests. They had found that concentrates of the infected material prepared by Petroff's method tended to wash off the cover slips, so they have devised a concentration technique using pancreatin (2·5% in a 1% aqueous sodium bicarbonate solution). Full details of this technique are given. In a preliminary investigation 149 specimens of sputum were concentrated in parallel by this method and by Petroff's method, and cultured on Loewenstein–Jensen medium. It was found that the pancreatin method yielded 43 positive results as opposed to only 38 by Petroff's technique, and also that the pancreatin method produced positive cultures in a shorter time than Petroff's method, sometimes by as much as 10 days.

The authors then describe in detail their microculture technique. Smears are made from the concentrates on cover glasses and incubated in 50% lysed horse blood containing 10 units per ml. of penicillin. Other media tried have been found to be less satisfactory. A comparison of the results obtained by this method of microculture and with those by culture on Loewenstein–Jensen medium showed that out of 193 specimens of concentrate there were 81 positive cultures by both methods and 8 positive cultures on Loewenstein–Jensen medium which were negative by the microculture method. Sensitivity tests are carried out by the microculture method by incorporating 1, 10, and 100 μg. of streptomycin, 10 and 80 μg. of PAS, and 0·2, 1, and 10 μg. of isoniazid per ml. in the media. The cover glasses are examined under the microscope for evidence of growth of the organisms, suitable controls being always incorporated in each test. Results are obtained in from 3 to 7 days, and details of the sensitivity tests on 21 organisms are given.

The authors suggest that this microculture method is reliable enough to produce a quick and accurate result in the majority of cases, and if cultures are made simultaneously on Loewenstein–Jensen medium the risk of failure to isolate *Myco. tuberculosis* is reduced to a minimum. *R. F. Jennison*

30. Slide Culture as a Means of Appraising the Streptomycin Sensitivity of Tubercle Bacilli in Sputum

P. J. COLLARD and P. G. MANN. *Journal of Clinical Pathology* [*J. clin. Path.*] **6**, 266–272, Nov., 1953. 3 figs., bibliography.

At Westminster Hospital Medical School, London, the authors investigated the suitability of slide cultures for the determination of sensitivity of tubercle bacilli in sputum to concentrations of 1 and 10 units of streptomycin per ml. of medium. They used half slides and the medium of Dubos and Noufflard (*Ann. Inst. Pasteur*, 1950, **78**, 208), but no concentration technique was employed. Full details of their technique are given.

Counts were made of the numbers of germinating and non-germinating bacilli, and the differences obtained in controls and tests were analysed statistically. In all, 16 positive cultures were obtained from 13 patients. The sensitivity of 8 strains was tested both by the microculture method and by tube culture. The authors conclude that slide cultures are too unreliable for routine use, although they confirmed the rapidity with which the results of sensitivity tests can be obtained by this method. They end their paper with a discussion of the use of slide cultures in the appraisal of bacterial sensitivity to drugs as a population characteristic.

[Although these authors found that slide cultures were unreliable they did not use a concentration technique and the medium employed was different from that used by Rice and Rowan (see Abstract 29).]

R. F. Jennison

31. The Development of Fluorescence Microscopy for Tubercle Bacilli and its Use as an Adjunct to Histological Routine

D. M. MCCLURE. *Journal of Clinical Pathology* [*J. clin. Path.*] **6**, 273–281, Nov., 1953. 2 figs., bibliography.

After an excellent review of the development of fluorescence microscopy since 1937 for the demonstration of tubercle bacilli, the author goes on to describe in detail the method he has used at the Victoria Infirmary, Glasgow, in the examination of tissue sections, for which he found an auramine–rhodamine staining solution to be much superior to simple auramine stains.

After satisfactory preliminary trials, 120 specimens of biopsy and surgical material were examined and tubercle bacilli were found in 39 of these. The 120 specimens were divided into groups according to the likelihood of the diagnosis of tuberculosis. In Group A (50 specimens) in which the histological appearances were diagnostic of tuberculosis, tubercle bacilli were found in 26. In Group B, of 13 specimens from cases in which tuberculosis was suggested histologically but not confirmed, 6 cases which were clinically suggestive gave positive findings, whereas the 7 which were not clinically suggestive showed no positive findings. Group C contained cases in which the histological appearance was not suggestive of tuberculosis, but tuberculosis was suspected clinically. In this group there were 2 positive findings out of 21 cases, and both of these had shown evidence of superadded pyogenic infection. In Group D (16 cases) there was no suggestion of tuberculosis histologically, and no tubercle bacilli were demonstrated. Group E consisted of 13 cases of sarcoidosis; 5 of these showed tubercle bacilli, and a review of the histology showed that the original diagnosis of sarcoidosis was doubtful.

The authors recommend the examination of tissue sections stained by the auramine–rhodamine method for its simplicity and for its speed in routine histological work. *R. F. Jennison*

Pharmacology

32. Plasma Iron Levels and Urinary Iron Excretion after the Intravenous Administration of Different Iron Preparations

J. A. NISSIM. *British Journal of Pharmacology and Chemotherapy* [*Brit. J. Pharmacol.*] **8**, 371–377, Dec., 1953. 2 figs., 9 refs.

In an investigation carried out at Guy's Hospital Medical School, London, rabbits were given large doses of organic iron complexes intravenously, and the concentration in the plasma and the rate of excretion of iron determined. Iron was estimated by a modification of the *ortho*phenanthroline method; the author emphasizes that the reagents must be used in adequate amounts for the large quantities of iron present after intravenous injection. The substances studied were preparations of iron rendered suitable for intravenous injection by combination with sugars and related organic substances. Excretion of iron was almost entirely in the urine, excretion by the bowel being negligible.

The preparations tested fell into three groups. The first, including such compounds as saccharated iron oxide, ferric glucosate, and "ferric chloride lactate", disappeared from the blood slowly and were also excreted slowly. Disappearance from the blood was due mainly to uptake by reticulo-endothelial cells. Some specimens of saccharated iron oxide gave lower plasma iron levels than the author's standard preparation, perhaps because iron was precipitated from these specimens at a *p*H closer to neutrality than the standard (3·7), so that some immediate precipitation may have taken place on intravenous injection. After the injection of colloidal ferric hydroxide, representing the second group, a rapid fall in plasma iron level was associated with massive precipitation, one rabbit dying 2 minutes after the injection. Urinary excretion was slow, only 0·27% of the dose being excreted in 24 hours.

The third group of preparations, typified by iron and ammonium citrate, "ferric chloride caramelate", and "ferric hydroxide ferrous ascorbate", disappeared rapidly from the blood and were excreted rapidly in the urine, 27·4% of a dose of ferric hydroxide ferrous ascorbate being excreted in 24 hours. Because of their high rate of diffusion into the tissues, these substances disappeared from the blood of animals in which the renal vessels were tied. *L. G. Goodwin*

33. Observations on the Diuretic Response to Parephyllin (R-3588), Neohydrin and Mercuhydrin when Administered Alone and in Combination

M. C. SILVERTHORNE and J. H. MOYER. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 83–93, Jan., 1954. 3 figs., 11 refs.

Many drugs have been used in combination with mercurial diuretics in an attempt to augment, either by additive or possibly by synergistic action, the effect of the mercurial compound. At Baylor University College of Medicine, Houston, Texas, the authors investigated the diuretic action of "paraphyllin" (diethylaminoethyl theophylline hydrochloride), a derivative of theophylline, given by mouth or parenterally either alone or in combination with the mercurial diuretics "mercuhydrin" (meralluride) or "neohydrin" (3-chloromercuri-2-methoxypropyluren) to a group of normal subjects and to patients in heart failure. Various combinations and schemes of administration of the drugs were tried, and these are described in some detail.

The results showed that parephyllin had only a transient diuretic effect when given alone by intramuscular injection, and when given in combination with mercuhydrin did not augment the effect of the latter substance. By oral administration also parephyllin did not have a significant diuretic action, either alone or when given in conjunction with the mercurial, neohydrin. Only when infused intravenously did parephyllin have a slight effect in increasing the diuretic action of mercuhydrin given intramuscularly. But intravenous injection of parephyllin caused dizziness, vertigo, nausea, and vomiting and offered no advantage over aminophylline. Neohydrin administered orally was an effective diuretic, but was only about one-half to three-fourths as effective as mercuhydrin, as judged by the degree of increase in water and sodium excretion. *R. Wien*

34. Effect of the Isomers of Amphetamine and Desoxyephedrine on Gastric Emptying in Man

D. W. NORTHUP and E. J. VAN LIERE. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **109**, 358–360, Nov., 1953. 4 refs.

In doses of ten milligrams each, D-amphetamine, L-amphetamine, and D-desoxyephedrine delay the emptying of the stomach in the human. L-Desoxyephedrine is without effect.—[Authors' summary.]

35. The Protective Action of Antihistaminic and Sympathomimetic Aerosols in Anaphylactic Microshock of the Guinea-pig

H. HERXHEIMER. *British Journal of Pharmacology and Chemotherapy* [*Brit. J. Pharmacol.*] **8**, 461–465, Dec., 1953. 12 refs.

Adrenaline and isoprenaline aerosols have an immediate relieving effect in bronchial asthma and are less likely to cause unpleasant side-effects than oral or subcutaneous doses. At University College Hospital Medical School, London, the author has investigated the effect of antihistaminic and sympathomimetic drugs given by inhalation as standardized aerosols upon anaphylactic shock in guinea-pigs sensitized to egg albumen. The drugs were administered before exposure to the shock-producing aerosol of egg albumen. The inhalation of a small amount of drug gave protection equal in degree to that of a much larger quantity given by intramuscular injection, but its duration was shorter, the protective effect

of antihistaminic aerosols disappearing in 2 hours, and of sympathomimetic amines in ½ hour. The explanation of the rapidity, potency, and evanescence of effect is probably that, when inhaled, the drug reaches a high concentration in a short time in the sensitized cells of the bronchial mucous membrane. By the time it has been distributed through the tissues the concentration is too low to be effective. When injected, the drug is widely distributed from the start and a larger dose must therefore be given, the effect of which persists until the drug is excreted or destroyed.

The protective potency and duration of action of the drugs tested in the guinea-pig corresponded to their observed clinical effects in man. Tripelennamine and promethazine were more potent than diphenhydramine and chlorcyclizine. Highly concentrated aerosols of antihistaminics or of ephedrine produced dyspnoea in guinea-pigs, possibly as a result of irritant action or of histamine release, which can be produced by antihistaminics under some conditions. Aminophylline aerosol had a weak protective action which was not increased by prolonging the period of inhalation or giving a higher concentration of drug. Given intraperitoneally, however, aminophylline gave more protection than any other drug tested. It is suggested that aminophylline has a different site of action, perhaps upon blood vessels other than the most superficial capillaries. *L. G. Goodwin*

36. **The Inhibition of Cholinesterases by Antagonists of Acetylcholine and Histamine**
A. TODRICK. *British Journal of Pharmacology and Chemotherapy* [*Brit. J. Pharmacol.*] **9**, 76–83, March, 1954. 2 figs., bibliography.

37. **Effects of N-Allylnormorphine upon the Respiratory Depression due to Morphine in Anesthetized Man, with Studies on the Respiratory Response to Carbon Dioxide**
C. M. LANDMESSER, S. COBB, and J. G. CONVERSE. *Anesthesiology* [*Anesthesiology*] **14**, 535–549, Nov., 1953. 4 figs., 34 refs.

The 9 subjects, all women, selected for this study of the effects of N-allylnormorphine were patients undergoing thyroidectomy at Albany Hospital (Union University), Albany, New York. They were prepared for surgery by hypodermic injection of morphine and scopolamine one hour before operation. Additional morphine was given intravenously before general anaesthesia was induced and maintained with nitrous oxide and oxygen (4:1½ litres per minute); in addition, 0·5% procaine was used locally by the surgeon. Immediately after operation a spirometer was attached to the anaesthetic machine in place of the breathing bag, and tracings were obtained of each patient's respirations during: (1) a control period; (2) a period of 5 minutes rebreathing while the carbon dioxide absorption canister was by-passed; (3) a 5-minute recovery period; (4) during the administration of 5 mg. of N-allylnormorphine intravenously and the response period of approximately 5 minutes which followed; and (5) during a second period of rebreathing while the carbon dioxide canister was again by-passed. From these records, the respiratory rate and minute volume at the end of each of the five test periods was measured directly, and the average tidal volume for the same time was calculated. Arterial blood samples were also obtained at the end of each test period. Blood pressure and pulse rate were measured approximately each minute during the experiment.

The initial average respiratory rate for all 9 patients was 9 per minute. Rebreathing carbon dioxide increased the respiratory rate by 44·4%, tidal volume by 78·8%, and minute volume by 193·1%. During the recovery period these figures returned approximately to control values. Hypoxia could not be demonstrated, in spite of the existing respiratory depression, but there was a significant elevation in the arterial blood carbon dioxide content in the control period. Rebreathing also caused an increase in the arterial carbon dioxide content, but not in the oxygen content.

The rapid intravenous injection of 5 mg. of N-allylnormorphine caused a return of respiration to normal rates within 30 to 60 seconds. The tidal volume increased for 1 or 2 minutes following the injection and then became stabilized after 5 minutes. The minute volume followed the tidal volume, but after stabilization it remained above the control value. There was a striking decrease in the arterial carbon dioxide content following the administration of N-allylnormorphine. The drug did not cause significant changes in blood pressure or pulse rate. The changes in respiratory rate, tidal volume and minute volume on rebreathing carbon dioxide after administration of N-allylnormorphine were similar in magnitude to those obtained before the injection.

The authors conclude that these results suggest that although the sensitivity of the respiratory centre, as tested by its response to carbon dioxide, before and after administration of the drug was similar, the centre responded at different thresholds. The respiratory stimulation beyond physiological levels after injection of N-allylnormorphine was attributed to the excessive concentration of carbon dioxide during the depression caused by morphine. These findings in general agree with those of other workers. *Norval Taylor*

38. **Effect of Levallorphan Tartrate upon Opiate Induced Respiratory Depression**
W. K. HAMILTON and S. C. CULLEN. *Anesthesiology* [*Anesthesiology*] **14**, 550–554, Nov., 1953. 2 figs., 7 refs.

In this study, reported from the State University of Iowa College of Medicine, 19 patients undergoing surgical procedures requiring minimal relaxation were divided into two groups. (1) Fourteen patients were anaesthetized with nitrous oxide–oxygen, supplemented with deliberate overdoses of one of three opiates, namely, "dromoran" (levorphan), pethidine, and morphine. When anaesthesia had been established, "levallorphan" tartrate was given intravenously in doses ranging from 1 to 5 mg. (2) In the other 5 cases the antagonist was given first, followed by the analgesic drugs given in appropriate doses and within such a period as was likely to cause respiratory depression. In all cases, the opiates were administered within a period not exceeding 20 minutes.

In Group 1 the effect of levallorphan was evident in one minute. An initial peak response was followed by some decrease in effect, but over a period as long as 4 hours respiratory depression never approached previously observed levels. It was notable that once respiration had returned to the initial rate, more levallorphan had no effect. In patients in Group 2, to whom levallorphan was given first, relatively large doses of opiates did not produce the expected respiratory depression.

The authors are satisfied that the administration of any one of these narcotics in combination with levallorphan tartrate can provide a supplement to nitrous oxide anaesthesia without the disadvantage of respiratory depression. Levallorphan when given before the analgesic drug appeared to be slightly sedative; it did not stimulate respiration, and no undesirable effects of the drug were noted. *Norval Taylor*

39. The Effectiveness of Oral Analgesics (Morphine, Codeine, Acetylsalicylic Acid) and the Problem of Placebo "Reactors" and "Non-reactors"

H. K. BEECHER, A. S. KEATS, F. MOSTELLER, and L. LASAGNA. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **109**, 393–400, Dec., 1953.

It is shown in this paper from the Massachusetts General Hospital (Harvard Medical School) that 600 mg. of aspirin by mouth produces a satisfactory analgesic effect, whereas 10 mg. of morphine sulphate or 60 mg. of codeine phosphate given orally are much less effective. The substances were given to surgical patients, usually about 30 hours after operation, and the effectiveness of the analgesia was judged from the patient's statements about pain and pain relief. Placebo and analgesic were given alternately in capsules every 2 hours and the patient was questioned every hour. Where no relief from pain was obtained after one dose of each, or a capsule was regurgitated, the drug was given parenterally and oral therapy resumed when the pain returned. A drug was considered analgesic only if pain relief was reported at both interviews after the dose. Patients found to have pain too severe for oral medication were omitted from the investigation. In assessing the results, only the effects of the first pair of doses were taken into account.

No. of Patients	Total Doses	Relief with Placebo %	Drug	Dose mg.	Relief %	
52	80	40	Aspirin	300	50	52
36	51	25·5	,,	600	54·9	
44	62	33·9	Codeine	60	38·7	40
40	54	31·5	Morphine	10	40·7	

Morphine and codeine could not be distinguished from the placebo under the conditions used.

The difference in effect between drug and placebo is statistically significant only for the group given 600 mg. of aspirin. Moreover, comparison of the combined results from both doses of aspirin (52% relief) with the combined results from morphine and codeine (40%) shows a difference significant only at the 6% level. However, if those patients who were relieved by the placebo are omitted from the analysis, the difference between the two combined groups becomes greater ($P=0{\cdot}028$), while the difference is even more obvious when the results from the 600-mg. dose of aspirin are compared with those from the opium alkaloids ($P=0{\cdot}02$). Thus it is possible to differentiate between the efficacy of different analgesics if only those subjects who do not react to a placebo are considered.

Reference is made to the finding of other workers of a significant difference between the response to codeine and to a placebo. The present method ignores slight (but real) analgesia, and a re-evaluation of such findings, excluding slight relief, gives results strikingly similar to those given here, showing that aspirin, but not codeine, is definitely superior to lactose in analgesic action by mouth. *Derek R. Wood*

40. Ganglionic Blocking Action of Atropine and Methylatropine

L. D. FINK and P. CERVONI. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol.*] **109**, 372–376, Dec., 1953. 4 figs., 8 refs.

Methylatropine is a quaternary nitrogen compound and might be expected to possess ganglionic blocking activity. Evidence of such activity was obtained by the authors, working at the University of Washington, Seattle, by recording the effects of atropine, tetraethylammonium (TEA), and methylatropine on contraction of the nictitating membrane induced by pre- and postganglionic stimulation, on the pressor response to bilateral occlusion of the carotid artery, and on the pressor response to the ganglionic stimulant DMPP (1:1-dimethyl-4-phenylpiperazinium iodide) in the anaesthetized cat.

The dose of each substance required to cause 50% depression of the response to preganglionic stimulation of the nictitating membrane was estimated, and methylatropine was shown to be about five times as active as TEA, 50% depression being produced by 0·19 mg of methylatropine per kg. body weight and by 1·0 mg. of TEA per kg. When the effects of atropine and TEA were compared, 1·9 mg. of atropine per kg. and 0·8 mg. of TEA per kg. caused 50% depression of the response. In these doses atropine also depressed the effect of postganglionic stimulation. When allowance was made for this (by inspection of the dose–response lines for both effects) the dose of atropine causing 50% depression of the effect of preganglionic stimulation was estimated to be 3·9 mg. per kg.; thus TEA has about five times the activity of atropine.

In depressing the carotid-sinus pressor reflex and the pressor effect of DMPP the range of activities was less wide. Methylatropine (1 to 2 mg. per kg.) was the most active, TEA intermediate (2 to 4 mg. per kg.), and atropine the least active. Thus 4 to 8 mg. of atropine per kg. effectively reduced the action of DMPP, but 4 mg. per kg. did not abolish the pressor reflex.

All three tests indicated that of these three drugs methylatropine has the greatest ganglionic blocking action and atropine the least. *Derek R. Wood*

Chemotherapy

41. **The Growth of *Candida albicans* during Antibiotic Therapy**

J. L. SHARP. *Lancet* [*Lancet*] **1**, 390–392, Feb. 20, 1954. 1 fig., 14 refs.

The effect of the administration of antibiotics on the normal microflora of the body, particularly in relation to the overgrowth of yeasts, has been the subject of several reports. At Knightswood Hospital, Glasgow, the author determined the frequency of *Candida albicans* infection in a series of 174 male patients suffering from pneumonia by examination of the sputum and of post-nasal and rectal swabs before, during, and after treatment with either "terramycin" (oxytetracycline) or sulphadiazine, the patients being allocated alternately on admission to one or other form of treatment. Oxytetracycline was given by mouth for 5 days to a mean total dose of 14·2 g., while the mean total dose of sulphadiazine, also given for 5 days, was 37 g.

In the whole series *Candida* was isolated on admission from 26% of throat swabs, 48% of specimens of sputum, and 3% of rectal swabs. In the patients treated with oxytetracycline the figures rose from 16 to 42% of the throat swabs, from 32 to 61% of sputum samples, and from *nil* to 59% of the rectal swabs. In the patients treated with sulphadiazine there was no increase in incidence during treatment, but 2 to 4 days after its cessation the percentage rose from 30 to 49% in the sputum and from 5 to 20% in the rectal swabs, possibly owing to cross-infection. In no case were there symptoms of moniliasis. The author points out that *Candida* was isolated on admission in a considerable proportion of cases; the sputum was the most fruitful source of the yeast, but the presence of *Candida* was not related to the age of the patient, the presence of chronic chest disease, or the type of infecting organism, suggesting that in the sputum *Candida albicans* is usually a harmless saprophyte. Nevertheless, many of the patients were discharged on the 14th day while still heavily infected with *Candida*, and exposure of young children in the home to moniliasis must be regarded as potentially dangerous. *R. Wien*

42. **The Effect of Pyrimethamine (Daraprim) on the Gametocytes and Oocysts of *Plasmodium falciparum* and *Plasmodium vivax***

P. G. SHUTE and M. MARYON. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [*Trans. roy. Soc. trop. Med. Hyg.*] **48**, 50–63, Jan., 1954. 9 figs., 6 refs.

At the Malaria Reference Laboratory of the Medical Research Council batches of mosquitoes (*Anopheles stephensi*) were fed on proved carriers of gametocytes of *Plasmodium falciparum* or *P. vivax* before, and at varying intervals after, the administration of 2·5 to 50 mg. of pyrimethamine. Most of the mosquitoes were dissected on the seventh day after the infected feed, when the oocysts were large enough to be seen and counted under the 2/3 objective. In infections with *P. vivax* a single dose of 50 mg. of pyrimethamine was sufficient to prevent the maturation of oocysts in mosquitoes which had been fed 2 hours after the carrier had taken the drug. With doses of 5 mg. or less little effect was noticeable. In infections with *P. falciparum* 25 mg. of pyrimethamine completely prevented the maturation of oocysts in mosquitoes fed as long as 144 hours after the drug had been taken by the carrier.

The authors had previously postulated that pyrimethamine and proguanil affect the female gametocyte only—a theory evolved to explain why the male gametocyte was capable of normal exflagellation despite exposure to the drug. They have now abandoned this theory in favour of the view that sporogony is prevented in the mosquito by failure of segmentation of the oocyst, and that these drugs act both on schizonts and sporonts at the stage of chromatin division. The potential value of such gametocyticidal drugs for malaria control is discussed.

[It would be more correct to call such drugs sporonticidal rather than gametocyticidal. Moreover, the statement that Foy and Kondi (*Trans. roy. Soc. trop. Med.*, 1952, **46**, 370) had proved pyrimethamine to be gametocyticidal is inaccurate, for these workers showed only that sporozoites were not to be found in the salivary glands of mosquitoes fed on gametocyte carriers treated with the drug.] *Clement Chesterman*

ANTIBIOTICS

43. **Sensitivity of the Cholera Vibrio to Antibiotics**

M. A. GOHAR. *Journal of Tropical Medicine and Hygiene* [*J. trop. Med. Hyg.*] **56**, 289–294, Dec., 1953. 11 refs.

The chemotherapy of cholera is much less well established than that of bacillary dysentery, although both diseases are local intestinal infections. In this study reported from the Kasr-el-Aini Faculty of Medicine, Cairo, the action of a number of antibiotics and sulphonamides on the cholera vibrio was investigated both *in vitro* and *in vivo*. The bacteriostatic effect of soluble compounds was determined in the following manner: 50 ml. of peptone water containing 1% glucose and 1% Andrade's indicator was inoculated with a 24-hour broth culture of *Vibrio cholerae*, 10 recently isolated strains of the Ogawa type being used. The medium was then distributed in tubes containing serial dilutions of the test drug. After incubation at 37° C. for 24 hours, readings were made of the highest dilution showing no fermentation of glucose; this was the minimum bacteriostatic concentration. For sparingly soluble compounds

a 10% suspension was made, and serial dilutions were prepared in melted agar and poured into plates. After infection and incubation at 37° C. the plates were examined for growth and the highest dilution showing absence of growth was recorded. Bactericidal action was determined as follows. To 1-ml. quantities of varying concentrations of the compounds equal quantities of a 24-hour broth culture of the cholera strain were added at room temperature. Tests were made at frequent intervals by withdrawing loopfuls which were seeded on broth and incubated at 37° C. for 24 hours.

In addition, experimental infections were induced in guinea-pigs by Koch's classic method. The animals were fed with the cholera vibrio after the stomach juice had been neutralized with sodium carbonate and the intestines immobilized by an intraperitoneal injection of tincture of opium. The test drugs were given in 2 doses of equal size one day before, or immediately after, or one day after, infection. The degree of infection in the animals was then assessed by examination of the stools for the cholera vibrio.

The antibiotics dihydrostreptomycin, chloramphenicol, aureomycin, and oxytetracycline had a more potent bacteriostatic action on *Vibrio cholerae* than the sulphonamides sulphaguanidine, sulphadiazine, "formocibazole", or sulphasuxidine. Only dihydrostreptomycin and formocibazole had an appreciable bactericidal effect. Resistance was readily acquired to dihydrostreptomycin, less readily to chloramphenicol, and least of all to aureomycin and oxytetracycline. In infections in guinea-pigs chloramphenicol and dihydrostreptomycin gave the best results when given either alone or in combination with sulphonamides. Treatment given only before infection and not subsequently was ineffective; for the treatment to be effective, therefore, it should be given without interruption during the whole period of exposure to the infection. *R. Wien*

44. **Effect of Combinations of Antibiotics on Lysis of *Staphylococcus aureus* by Penicillin**

W. M. M. KIRBY and J. M. BURNELL. *Journal of Bacteriology* [*J. Bact.*] **67**, 50–52, Jan., 1954. 3 figs., 9 refs.

When penicillin in a concentration of 0·1 unit per ml. is added to a diluted culture of *Staphylococcus aureus* turbidity at first increases as a result of swelling of the organisms, but after a few hours it decreases, becoming minimal at 10 hours; this decrease is caused by lysis. At the University of Washington, Seattle, the effect of combinations of antibiotics in the killing and lysis of staphylococci was studied. It was found that the addition to the culture with the penicillin of increasing concentrations of chloramphenicol up to 80 μg. per ml. caused a progressive delay in lysis; moreover the initial increase in turbidity was greater than it was with penicillin alone. The delay in lysis was associated with a decrease in the rate of killing of the organisms. Similar changes were observed when aureomycin and oxytetracycline were added to the penicillin. It is suggested that lysis is the result of the action of autolytic enzymes upon dead bacteria. *D. G. ff. Edward*

45. **Sensitivity of *Pseudomonas aeruginosa* to Antibiotics.** [In English]

M. E. PARMALA. *Annales medicinae experimentalis et biologiae Fenniae* [*Ann. Med. exp. Biol. Fenn.*] **31**, 267–274, 1953. 8 refs.

In this study carried out at the University of Helsinki the author performed tests of the sensitivity of some 60 strains of *Pseudomonas aeruginosa* (obtained from samples of pus, urine, faeces, and sputum) to polymyxin B, bacitracin, neomycin, "terramycin" (oxytetracycline), and "gantrisin" (sulphafurazole) by means of the moistened-paper-disk technique in Petri dishes. Readings were taken after an incubation period of 20 hours at 37° C.

Neomycin alone proved effective against all strains, showing an inhibition zone 2 mm. in diameter when used in a concentration of 10 mg. per ml. of medium. Just under 50% of the strains were sensitive to polymyxin B, and only 20% to bacitracin. Sulphafurazole did not completely inhibit growth of any of the strains, but caused partial inhibition in 33% of the strains. Oxytetracycline was found to be even less active by the technique employed, causing slight inhibition of only 28% of strains.

Despite these results, the author considers that the nephrotoxicity of neomycin and polymyxin B restricts their use to the treatment of urgent cases only or to local application. In view of its low toxicity, he recommends sulphafurazole as the drug of choice for the initial routine treatment of *Pseudomonas* infections of the urinary tract. *D. Geraint James*

46. **Antibiotic Combinations and Resistance to Antibiotics. Development of Resistance during Repeated Subcultures of Staphylococci and Certain Streptococci on Media Containing Penicillin, Streptomycin, Erythromycin, Terramycin, and Chloramphenicol Used Singly and in Pairs**

S. S. WRIGHT, E. M. PURCELL, C. WILCOX, M. K. BRODERICK, and M. FINLAND. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **42**, 877–895, Dec., 1953.

Increasing proportions of the staphylococci isolated from infective material are proving to be resistant to penicillin and other antibiotics. Although erythromycin is highly active against such resistant staphylococci, the organisms readily develop resistance to this agent too *in vitro* or during treatment. The authors have shown (*Proc. Soc. exp. Biol.* (*N.Y.*), 1953, **82**, 124; *Abstracts of World Medicine*, 1953, **14**, 190) that this process can be delayed or depressed *in vitro* by the use of a combination of erythromycin with penicillin or streptomycin or both. They now report further work carried out at the Boston City Hospital (Harvard Medical School) on the development of resistance by staphylococci, and also by enterococci and a strain of *Streptococcus viridans*, to various antibiotics in pairs. The organisms tested were all originally isolated from infected material from human patients, and the strain used with each pair of antibiotics was equally sensitive to both of them. A heart-infusion agar medium with 10% defibrinated horse

blood was employed and the antibiotics were mixed in constant proportions. Observations were made on 6 pairs of antibiotics, each pair being tested against 8 or 9 strains, and 4 parallel series of subcultures being made—on antibiotic-free medium, on media containing graded concentrations of each of the individual antibiotics, and on media containing graded concentrations of the combination. The results are expressed graphically to show the successive changes in resistance of each of the strains to the individual antibiotics and to the pair in each case. Cross-resistance tests were carried out at intervals during each experiment and after the last (25th) subculture.

On exposure to penicillin and streptomycin separately staphylococci and enterococci became rapidly more resistant to both and *Str. viridans* became resistant to the latter, but its resistance to the former increased slowly and only slightly. On exposure to a mixture of penicillin and streptomycin (1:256), staphylococci and enterococci showed a steady increase in resistance to the mixture, but at a slower rate than to the individual agents, while the resistance of the streptococcus to the mixture increased at the same rate as to penicillin alone. Exposure to the mixture caused a marked increase in the resistance of staphylococci to both individual components, of the enterococci to streptomycin only, and of the streptococci to penicillin only. No cross-resistance was observed to other antibiotics.

Exposure to oxytetracycline alone caused an increase in resistance in staphylococci and enterococci, but not in the streptococcus. Exposure to a mixture of penicillin and oxytetracycline (1:16) caused an increase in resistance to the mixture in the first two organisms which was only slightly less than that observed with oxytetracycline alone. Again no cross-resistance was observed to develop.

The resistance of each strain to erythromycin alone increased rapidly and markedly. Resistance to a mixture of erythromycin and oxytetracycline (1:2) increased in staphylococci and enterococci in the same way as to the latter drug alone, and in the streptococcus in the same way as to the former drug. Resistance to the individual antibiotics increased to varying degrees in the different strains, but no cross-resistance developed except to carbomycin in strains developing erythromycin resistance and to aureomycin in strains developing oxytetracycline resistance.

Exposure to chloramphenicol alone caused a moderate increase in resistance in enterococci, but little or none in staphylococci or *Str. viridans*. Similar increases were observed in resistance to a mixture of this drug with streptomycin, but none developed to mixtures with penicillin or erythromycin, although exposure to these mixtures increased the resistance of more than half the strains to the individual components. Again no cross-resistance was observed.

In the discussion of their findings the authors emphasize the exploratory nature of this work and point out that the proportions of each antibiotic in the pairs were arbitrarily chosen and may have been an important factor in determining the results. No relation between the effect of combination in delaying or suppressing the development of resistance and the problems of synergism and antagonism is apparent from these studies, and no light is shed on the difference between penicillin-resistant organisms isolated from patients (invariably penicillinase producers) and those resulting from exposure *in vitro* (which are equally resistant, but do not produce penicillinase).

Malcolm Woodbine

47. Successful Treatment of Intestinal Moniliasis with Fatty Acid–Resin Complex

I. NEUHAUSER. *Archives of Internal Medicine* [*Arch. intern. Med.*] **93**, 53–60, Jan., 1954. 1 fig., 30 refs.

The appearance of large numbers of the organism *Candida albicans* in the faeces, together with various untoward symptoms, is frequently noted in patients receiving certain antibiotics, especially oxytetracycline (" terramycin ") and aureomycin. Usually the symptoms rapidly disappear and the number of *C. albicans* in the faeces diminishes after the antibiotic has been withheld, but in a few cases intestinal moniliasis persists and often proves difficult to treat successfully. While undecylenic acid is an effective antimycotic, it causes severe (though not dangerous) toxic symptoms when given orally in larger doses. In an attempt to find a new type of therapeutic agent, the authors, working at the University of Illinois School of Medicine, tried combining undecylenic acid with an anion-exchange resin. Such complexes, finely powdered, have been shown in animals to coat the walls of the stomach and accumulate near the intestinal walls, undergoing slow hydrolysis with continuous release of the drug at a rate dependent on the strength of the resin, that of the acid drug, the *p*H of the environment, and the size of the powder particles.

The successful treatment of a patient with severe intestinal moniliasis with a very finely powdered undecylenic-acid–resin complex without untoward symptoms prompted them to investigate the growth-inhibiting properties of resin complexes with other fatty acids on *C. albicans* cultured in Sabouraud's glucose agar at *p*H 5·6 and 7·5. They found that a caprylic-acid–resin complex was the most effective complex of this type, inhibiting the growth of *C. albicans* in both acid and alkaline media.

Two further cases of intestinal moniliasis are reported which have been successfully treated, without any undesirable side-reactions, with a caprylic-acid–resin complex in doses of 2 to 4 capsules 4-hourly, each capsule containing 250 mg. of the acid–resin complex, of which the caprylic acid content was 115 to 121 mg.

A. Ackroyd

48. Laboratory and Clinical Findings in Patients Treated with Carbomycin

A. H. KUTSCHER, J. D. PIRO, E. V. ZEGARELLI, S. L. LANE, and L. SEGUN. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **3**, 1194–1203, Dec., 1953. 8 refs.

Carbomycin was used in the treatment of 15 patients, most of whom were undergoing mass dental extractions or had dental or oral infections, while one had rheumatic heart disease and required oral surgery. With the exception of one patient with a urinary infection and two with infection following dental extraction, all these

patients were given the drug with the object of preventing postoperative infection. Administration of carbomycin, 500 mg. 6-hourly, was begun 24 hours before operation and continued for varying periods thereafter. Treatment was judged to be successful in all cases and there were no serious side-effects. Detailed laboratory studies showed no evidence of any deleterious effect.

T. Anderson

49. **Tetracycline, a New Antibiotic**

L. E. PUTNAM, F. D. HENDRICKS, and H. WELCH. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **3**, 1183–1186, Dec., 1953. 5 figs., 4 refs.

In an attempt to reduce the toxic effects of aureomycin (chlortetracycline) the chlorine atom has been removed from the molecule to give tetracycline, which is more soluble and more stable than aureomycin and oxytetracycline (" terramycin "). The pharmacological properties and antibacterial activity of the three cyclines are generally similar. With a dose of 500 mg. 6-hourly there is a gradual rise in the mean blood concentration, which eventually becomes stabilized after 24 hours at between 3 and 5 μg. per ml. In preliminary tests carried out by the U.S. Food and Drug Administration 217 healthy adult males were given a dose of 2 g. a day for 3 days. Nausea developed in 10 subjects and vomiting in one, 4 showed evidence of a sensitization reaction in the skin, 6 complained of generalized itching, and 12 of pruritus ani. Gastrointestinal complaints were fairly frequent: there was one example of frank diarrhoea and 58 of loose stools, while 50 subjects complained of flatulence. It seemed possible that these toxic effects were more common when the antibiotic was given as a tablet than in a capsule.

The material was used for the treatment of a miscellaneous group of infections in 32 cases with apparent efficacy. *T. Anderson*

50. **Clinical and Laboratory Observations of a New Antibiotic, Tetracycline**

M. FINLAND, E. M. PURCELL, S. S. WRIGHT, B. D. LOVE, T. W. MOU, and E. H. KASS. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **154**, 561–568, Feb. 13, 1954. 2 figs., 11 refs.

This important communication from Harvard Medical School gives an early and authoritative survey of the laboratory and clinical properties of tetracycline hydrochloride (an antibiotic prepared by the catalytic hydrogenation of aureomycin (chlortetracycline)) in comparison with those of aureomycin and oxytetracycline (" terramycin "), and demonstrates its therapeutic value in a group of cases of respiratory and urinary infections.

Tetracycline hydrochloride appears to be more stable in solution than its analogues, particularly aureomycin, which undergoes marked deterioration quite rapidly. The range of antibacterial action of the new antibiotic is very similar to that of aureomycin and of oxytetracycline, and complete cross-resistance is found in organisms made resistant by exposure to any one of the three *in vitro*. Satisfactory concentrations in the blood and urine are obtained with oral doses of 250 to 500 mg. of tetracycline hydrochloride 6-hourly. A concentration in the cerebrospinal fluid of $\frac{1}{8}$ to 1/32 of that in the blood was found following a single intravenous injection of 0·5 to 1 g. of tetracycline in patients without meningitis; it appeared to be demonstrable more regularly than its analogues in the spinal fluid.

The effect of tetracycline in the control of 118 cases of acute respiratory or urinary infection was considered to be equal to that of its analogues. It was given in various dosages, both orally and intravenously, though for practical purposes the optimum dose will probably be of the same order as that of oxytetracycline and aureomycin. The incidence of untoward gastrointestinal symptoms was markedly less with tetracycline than with the other two drugs. *D. Geraint James*

51. **Efficacy and Toxicity of Oxytetracycline (Terramycin) and Chlortetracycline (Aureomycin). With Special Reference to Use of Doses of 250 mg. Every Four to Six Hours and to Occurrence of Staphylococcic Diarrhea**

M. FINLAND, M. E. GRIGSBY, and T. H. HAIGHT. *Archives of Internal Medicine* [*Arch. intern. Med.*] **93**, 23–43, Jan., 1954. 24 refs.

The occurrence of diarrhoea with or without upper gastrointestinal symptoms has been noted comparatively frequently in patients receiving oxytetracycline (" terramycin ") or aureomycin. The authors analyse the results of treating, at Boston City Hospital (Harvard Medical School), 236 patients suffering from various diseases—chiefly from infections of the respiratory or urinary tracts—with oxytetracycline and 284 similar patients with aureomycin, usually in doses of 250 mg. every 4 or (preferably) 6 hours. Although no conclusions could be drawn with respect to the efficacy of this dosage as compared with the larger dosages which have previously been used, satisfactory clinical and bacteriological results were obtained in most acute infections with both drugs. Gastric symptoms alone occurred in 10·2% of those patients receiving oxytetracycline and in 6·7% of those receiving aureomycin, while severe watery diarrhoea occurred in 18·6% of the former and in 9·5% of the latter. With both drugs the incidence of diarrhoea was about twice as frequent amongst those patients receiving 4-hourly treatment as it was amongst those receiving the same dosage 6-hourly. *Staphylococcus aureus* was the predominant organism in the stools of 20 out of 26 patients who were receiving 250 mg. of oxytetracycline 4-hourly and of 6 out of 10 patients who were receiving the same dosage of the drug 6-hourly. This organism was cultured from the stools of only 4 of 22 patients receiving aureomycin, all of whom were receiving the drug 4-hourly. The diarrhoea subsided and the normal flora returned to the stools rapidly in most cases when the administration of the offending drug was discontinued without other than supportive treatment. It was noted that the use of cathartics was often associated with the initiation of severe diarrhoea.

The authors consider that a dosage of 250 mg. of these drugs given 6-hourly will reduce the incidence of the untoward effects associated with them and will probably not reduce their therapeutic efficacy. *A. Ackroyd*

52 (*a*). **The International Standard for Aureomycin**
J. H. HUMPHREY, J. W. LIGHTBOWN, M. V. MUSSETT, and W. L. M. PERRY. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] **9**, 851–860, 1953. 1 fig., 6 refs.

52 (*b*). **The International Standard for Bacitracin**
J. H. HUMPHREY, J. W. LIGHTBOWN, M. V. MUSSETT, and W. L. M. PERRY. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] **9**, 861–869, 1953. 1 fig., 4 refs.

In these two papers from the Department of Biological Standards, National Institute for Medical Research, London, the authors report the results of, and describe the methods employed in, the establishment, on the authorization of the World Health Organization, of international standards for aureomycin and bacitracin. Six laboratories in five different countries collaborated in these assays, their results being then sent to London where they were analysed statistically.

In all, 30 assays of 100 g. of a single batch of aureomycin hydrochloride were carried out, 26 by biological methods and 4 by physico-chemical methods. This substance, proposed for adoption as the international standard for aureomycin, was compared with the standard preparation held by the United States Food and Drug Administration (F.D.A.) in relation to which it was shown to have a potency of 101·39%. Since the material used in establishing the international standard may not have been 100% pure and probably contained a small quantity of inert material, it was considered desirable to establish a unit notation as well, though not necessarily for use in practice. The international unit of aureomycin was therefore defined as the activity obtained with one microgramme of the international standard substance.

Similarly, 52 assays were carried out on bacitracin, 48 by biological methods and 4 by the Hiscox physico-chemical method, the proposed international standard being compared with the existing working standard for bacitracin of the United States F.D.A. The substance adopted as the international standard for bacitracin is defined as containing 55 international units of activity per mg., and the international unit of bacitracin has therefore been defined as the activity contained in 0·0182 mg. of the international standard substance.

A. W. H. Foxell

CHEMOTHERAPY OF TUBERCULOSIS

53. **Tubercle Bacilli Resistant to Isoniazid. Virulence and Response to Treatment with Isoniazid in Guinea-pigs**
D. A. MITCHISON. *British Medical Journal* [*Brit. med. J.*] **1**, 128–130, Jan. 16, 1954. 7 refs.

In an investigation into the relationship between the virulence of tubercle bacilli and their sensitivity or resistance to isoniazid, 8 pairs of sensitive and resistant strains from the sputum of 8 tuberculous patients (the sensitive strains being obtained before treatment with the drug) were injected separately into groups of guinea-pigs at the Postgraduate Medical School of London. By subculturing resistant strains on slopes containing 0·2, 10, or 50 μg. of isoniazid per ml., admixture of the strain with organisms of a lower degree of resistance was avoided. Each strain was injected into 6 guinea-pigs, 3 of the animals being left untreated and 3 receiving 4 mg. of isoniazid per kg. body weight per day. Pairs of guinea-pigs were killed after 6, 10, and 14 weeks and the extent of tuberculous disease estimated quantitatively.

The resistant strains were recovered at necropsy, and none of them showed any alteration in degree of resistance. It was found that an increase in resistance to isoniazid was associated with a decrease in the virulence of the strain. Evidence was also found to suggest that with the more virulent of the resistant strains, resistance was increased by treatment of the host with isoniazid between the 10th and 14th weeks after infection.

[The abstracter had difficulty in reconciling the results of the quantitative sensitivity tests (shown in Table II of the original paper) with the figures for the minimal inhibitory concentration of isoniazid for the various strains (given in Column 1 of Table III).]

John M. Talbot

54. **The Enzymic Inactivation of Isoniazid in Animals and Man.** (Enzymatische Inaktivierung von Isonicotinsäurehydrazid im menschlichen und tierischen Organismus)
R. BÖNICKE and W. REIF. *Archiv für experimentelle Pathologie und Pharmakologie* [*Arch. exp. Path. Pharmak.*] **220**, 321–333, 1953. 5 figs., 6 refs.

The elimination of isoniazid from the organism was studied by the authors, using microbiological and chemical methods, both in normal healthy individuals and in patients with tuberculosis. They point out that the method of Kelly and Poet (*Amer. Rev. Tuberc.*, 1952, **65**, 484) for the estimation of isoniazid in the urine is not specific, including in addition to free, tuberculostatically active isoniazid, metabolic products with substituted free amino groups which are inactive chemotherapeutically. They have therefore simplified and increased the sensitivity of the method by omitting the stage of hydrolysis by boiling in an acid medium.

It was found that isoniazid was excreted unchanged in the urine in the unaltered form only to a small extent (about 12·4% of the dose), the remainder being recovered in a bound form. It was not possible to discover in which organ conversion to the bound form took place. About 20 to 30% of the dose was converted to *iso*nicotinic acid. Experiments performed on rabbits showed that the liver was capable of partially converting isoniazid to *iso*nicotinic acid, whereas other tissues (lung, spleen, kidneys, and muscle) were unable to perform this function. There was a direct relation between the concentration of isoniazid in the blood and the amount excreted in the urine. *R. Wien*

55. **Elaiomycin, a New Tuberculostatic Antibiotic. Isolation and Chemical Characterization**
T. H. HASKELL, A. RYDER, and Q. R. BARTZ. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **4**, 141–144, Feb., 1954. 2 figs.

56. **The Antimycobacterial Activity of a Peptide Preparation Derived from Calf Thymus**
R. J. DUBOS and J. G. HIRSCH. *Journal of Experimental Medicine* [*J. exp. Med.*] **99**, 55–63, Jan. 1, 1954. 8 refs.

Extraction of calf thymus with aqueous ethanol was found by the authors to yield fractions possessing high activity against the growth of acid-fast bacteria. This antibacterial effect was studied at the Rockefeller Institute for Medical Research, New York, by adding serial dilutions of such an extract to a synthetic fluid medium and inoculating with various strains of tubercle bacilli maintained in standard " tween "–albumin media.

Different strains of mycobacteria varied considerably in their sensitivity to the growth inhibition caused by the thymus extract [thymus peptide; see Abstract 57], an attenuated strain of bovine tubercle bacillus (B.C.G.–Phipps), which was inhibited by as little as 1 μg. of thymus peptide per ml. of medium, being the most sensitive organism examined. The virulent human and bovine strains tested were about 10 times more resistant, and the avirulent human strain H37Ra, one avian strain, and a saprophytic mycobacterium required from 30 to 100 μg. per ml. for inhibition.

The effect of thymus peptide on non-acid-fast organisms was also studied. High concentrations of the peptide (300 μg. per ml.) inhibited *Staphylococcus aureus* and *Bacillus brevis*, while amongst the organisms insensitive to as much as 1 mg. per ml. were *Klebsiella pneumoniae*, *Salmonella typhimurium*, *Shigella dysenteriae*, *Bacterium coli*, *Proteus vulgaris*, *Streptococcus haemolyticus*, and *Streptococcus faecalis*. The size of the bacterial inoculum had no effect on the activity of thymus peptide when the final concentration of microorganisms was 10^{-3}, 10^{-4}, or 10^{-5} of a full-grown culture of tubercle bacilli. With inocula larger than this, however, the activity was moderately reduced. The activity of the peptide increased with increasing alkalinity of the medium, while a final concentration of 0·1% of casein hydrolysate or of 10% beef heart infusion broth reduced its activity against tubercle bacilli approximately 100-fold. " Tween-80 " did not affect its activity.

Thymus peptide was not found to exert a rapid bactericidal action on tubercle bacilli, but organisms exposed to it for longer than 2 weeks could not afterwards be made to multiply in ordinary culture media. Substances similar to thymus peptide were extracted from calf spleen, sheep thymus, beef lymph nodes, and calf pancreas, but not from calf lung or calf liver. It is thought possible that substances of this type may be released in areas of inflammation or necrosis, and may account, at least in part, for the limitation of growth of tubercle bacilli often observed in certain caseous areas. *R. B. Lucas*

57. **Chemical Studies on a Basic Peptide Preparation Derived from Calf Thymus**
J. G. HIRSCH and R. J. DUBOS. *Journal of Experimental Medicine* [*J. exp. Med.*] **99**, 65–78, Jan. 1, 1954. 11 refs.

The authors give an account of the chemical properties of the thymus peptide, the antibacterial properties of which were described in their previous paper [see Abstract 56]. The substance is prepared by extraction of minced calf thymus with hydrochloric acid, followed by treatment with sodium hydroxide, picric acid, and acetone, yielding a powder varying in colour from tan to white which is soluble in water (up to concentrations of 1%) and in the lower alcohols, the solubility being minimal between *p*H 10 and 11. Solutions at *p*H 7 retained their antibacterial properties after autoclaving at 15 lb. per sq. inch (1 kg. per sq. cm.) for 15 minutes, though acid or alkaline solutions lost such properties after 45 minutes at the same pressure. Incubation with trypsin likewise abolished antibacterial activity, but pepsin was without effect.

The results of qualitative chemical examination indicated that the thymus factor is a protein or proteins, probably containing arginine, tryptophane, and tyrosine, but no carbohydrate or phosphorus, and dialysis experiments showed that the size of the molecule is relatively small. The results of quantitative analysis are also given. It is finally concluded that the substance is a basic peptide or a mixture of such peptides. *R. B. Lucas*

58. **Mechanisms Involved in the Antimycobacterial Activity of Certain Basic Peptides**
J. G. HIRSCH. *Journal of Experimental Medicine* [*J. exp. Med.*] **99**, 79–88, Jan. 1, 1954. 10 refs.

In further experiments carried out at the Rockefeller Institute for Medical Research, New York, varying concentrations of thymus peptide, a substance which inhibits the growth of tubercle bacilli *in vitro* [see Abstracts 56 and 57], were added to suspensions of an attenuated strain of bovine tubercle bacillus (B.C.G.–Phipps) in a synthetic fluid medium. Other substances were then added, and the effect on the activity of thymus peptide was noted. Heparin caused a slight reduction in activity, but similar concentrations of other acidic tissue substances (thymus and yeast nucleic acids) and of basic compounds (cadaverine and arginine) were without effect. Beef heart infusion broth, however, diminished the activity of thymus peptide about 30-fold, and this inhibitory action was not affected by treatment with acid or alkali or heating to high temperatures, suggesting that the substances responsible for the antagonism were more likely to be inorganic than organic. Thymus peptide was also found to be about 10 times less active in a medium made up with tap-water than in one made with distilled water, a phenomenon thought to be due to the inhibitory action of sulphate ions in the tap-water medium. Further investigation with numerous metal salts showed that organic sulphur-containing compounds were less inhibitory than inorganic sulphates.

Various basic peptides, including polylysine and pituitary adrenocorticotrophic hormone, were tested for antimycobacterial activity, and were found to be only slightly less active than thymus peptide, and as in the case of that substance, this activity was also antagonized by sulphate ions.

It is suggested that thymus peptide suppresses the growth of tubercle bacilli by interfering with the normal sulphur metabolism of these organisms.

R. B. Lucas

Infectious Diseases

59. **Preliminary Report on the Therapeutic Action of Methymycin in *Brucella melitensis* Infection**
G. C. MAX and D. MENDEZ. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **4**, 83–86, Jan., 1954. 4 figs.

" Methymycin ", a new antibiotic similar to aureomycin and reported to have significant activity against *Brucella* organisms *in vitro*, was used at the Contagious Diseases Hospital, Mexico City, in the treatment of 4 cases of acute brucellosis. All the patients were males and ranged in age from 6 to 35 years.

After periods of illness of variable duration, treatment was started with a dose of 2 g. of methymycin daily, later reduced to 1·5 g. daily until a total of 50 to 60 g. had been given. In each case the temperature fell rapidly to normal, although slight irregularities recurred occasionally. Symptoms disappeared within 8 days in 3 cases and in 15 days in the remaining case. Blood cultures rapidly became negative in 3 cases; in the fourth there was still a positive culture on the 15th day, but it had become negative by the 30th day. Neither the erythrocyte nor leucocyte counts changed appreciably, nor did the agglutination titres diminish in those cases in which the initial value was high. No toxic manifestation attributable to methymycin or evidence of intolerance was observed.

The authors point out that because of the occasional temperature irregularities and the positive blood culture in one case, methymycin cannot be considered to have a definite curative effect, and in fact report in an addendum to the paper that 3 of the 4 cases have relapsed.

D. J. Pearce

60. **A Study of the Relationship of the Absence of Tonsils to the Incidence of Bulbar Poliomyelitis**
L. WEINSTEIN, M. L. VOGEL, and N. WEINSTEIN. *Journal of Pediatrics* [*J. Pediat.*] **44**, 14–19, Jan., 1954. 18 refs.

To determine whether the bulbar form of poliomyelitis is more frequent in patients whose tonsils and adenoids have been removed than in patients who have not been so treated, the authors reviewed the case records of 800 patients with poliomyelitis admitted to the Haynes Memorial Hospital, Boston. In 500 of these cases tonsils and adenoids had been removed at some time and in 300 they had not. In all cases the clinical history, the physical findings, and the changes in the cerebrospinal fluid were consistent with the diagnosis of poliomyelitis. It was found that the incidence of the bulbar form of the disease was higher in patients who had undergone adeno-tonsillectomy, regardless of the time of operation, than in the others. Of 85 patients with bulbar poliomyelitis and 80 with bulbo-spinal poliomyelitis, 73 and 67 respectively had had tonsils and adenoids removed. In fact, all forms of poliomyelitis were more common in patients who had been operated on. Age and sex did not appear to be significant factors.

The authors' findings confirm those of Top and of Lucchesi and LaBoccetta. It is suggested that since the incidence of the disease is not related to the time of operation, absence of the tonsils is more important as an aetiological factor than local trauma.

David Morris

61. **Ilotycin (Erythromycin) in the Treatment of A Prime Influenza**
G. A. CRONK and D. E. NAUMANN. *New York State Journal of Medicine* [*N.Y. St. J. Med.*] **54**, 373–375, Feb. 1, 1954. 2 figs.

The value of erythromycin in the treatment of A-prime influenza was investigated at the Infirmary of Syracuse University, New York. Between January and March, 1953, a total of 263 [*sic*] patients with clinical influenza were admitted to the hospital, and of these, 89 were given erythromycin in a dosage of 200 mg. 4 times a day, 91 received an analgesic, and 61 a placebo. Influenza A-prime virus was isolated from the throats of 82% of all the patients, confirmation being obtained by complement-fixation and haemagglutination tests.

There was no significant difference between the three groups in respect of response of temperature to treatment or average length of stay in hospital. In both control groups there was a transient recurrence of pyrexia on the fourth day after admission which was not observed in the erythromycin-treated group. The authors are unable to explain the significance of this, because there was no evidence of secondary bacterial infection in any of the cases in the series.

D. Geraint James

62. **The Winter Vomiting Disease. A Report from General Practice**
J. F. GOODALL. *British Medical Journal* [*Brit. med. J.*] **1**, 197–198, Jan. 23, 1954.

During the period January to March, 1953, 46 patients were seen in a general practice in Skipton, Yorkshire, whose main complaint was of sudden and severe vomiting. The typical history was of sudden onset of nausea and vomiting, accompanied by epigastric pain and followed by passage of a few loose stools. The patients were of all ages, and recovery was complete within 48 hours. The condition did not appear to be very infective since 35 of the patients came from different households. Complement-fixation tests for influenza viruses A and B were carried out in 9 cases during and after the illness, but no alteration in titre was observed. Bacteriological examination of the faeces in 6 cases did not reveal any pathogenic organisms. It is held that this is a specific disease of unknown aetiology, and that the cases provide no evidence for the existence of so-called " gastric 'flu ".

Bernard Isaacs

Tuberculosis

63. Intrathecal Fibrinolysis with Streptokinase in Tuberculous Meningitis

A. P. FLETCHER. *Journal of Clinical Investigation* [*J. clin. Invest.*] **33**, 69–76, Jan., 1954. 2 figs., 15 refs.

At St. Mary's Hospital, London, the author carried out a quantitative laboratory investigation to determine the potential value of streptokinase in the treatment of tuberculous meningitis. Streptokinase itself has no fibrinolytic properties, acting on serum plasminogen to form a fibrinolytic enzyme, plasmin; the action of both streptokinase and plasmin may be inhibited by naturally-occurring antibodies. Measurements of the components of this system were therefore undertaken in cerebrospinal fluid (C.S.F.) from normal subjects and from patients with tuberculous meningitis.

The plasminogen content of the latter (71 specimens from 26 patients) was much higher than that of normal C.S.F. (10 specimens), and that of the lumbar was higher than that of the ventricular fluid. Very high plasminogen levels were found in the lumbar C.S.F. of 8 patients with spinal block. Antiplasmin was present in all of 28 specimens of C.S.F. from 18 cases of tuberculous meningitis and in 12 normal specimens, its concentration in the former also being higher than that in the latter and the highest concentration being found in the lumbar fluid, but in all specimens the antiplasmin content was small in comparison with that of plasmin. However, since the rate of conversion of plasminogen to plasmin in the presence of optimal concentrations of streptokinase is reduced by high concentrations of plasminogen, the relative importance of a comparatively low antiplasmin content is increased in such circumstances, and " fluids of high plasminogen content have only a small lytic potentiality ". This was found to be the case in 56 specimens of C.S.F. from 23 patients with tuberculous meningitis, the addition to which of small quantities of streptokinase *in vitro* resulted in no fibrinolytic activity at all, while the quantity of streptokinase which produced some lytic activity when added to the C.S.F. *in vitro* corresponded to an intrathecal dose *in vivo* of 2,500 to 15,000 Christensen units.

In experiments *in vivo*, owing to the systemic and local irritative effects of large doses of streptokinase, a low level of fibrinolytic activity only was aimed at, the dose of streptokinase given being that which was calculated to yield 1 unit of plasmin activity per ml. of C.S.F. in each case and ranging between 300 and 3,000 units. However, the maximum enzyme activity of the C.S.F., reached 10 to 30 minutes after the injection, was in fact much less than had been calculated, and in some cases in which very large doses of streptokinase were injected below a spinal block no free fibrinolytic activity was produced at all. The discrepancy between calculated and observed activity was much less when the dose indicated was relatively small. It is suggested that the irritative effect of streptokinase in high concentrations upon the spinal theca causes an inflow of serous fluid with a high concentration of inhibitor which may nullify its potential therapeutic action; thus a routine dose of 100 Christensen units is likely to produce no free enzyme in a substantial proportion of cases. In 9 cases of tuberculous meningitis 25 attempts were made to lyse existing spinal blocks by the intrathecal injection of streptokinase, with only one temporary success.

[These careful and exhaustive laboratory tests appear to confirm and partly explain the conclusions reached by the abstracter from a controlled therapeutic trial (*Lancet*, 1951, **1**, 1334; *Abstracts of World Medicine*, 1951, **10**, 325) that streptokinase is useless and dangerous in the treatment of tuberculous meningitis. It is surprising, therefore, to read the author's conclusion that " streptokinase may be used with reasonable chance of success, either prophylactically, or for the treatment of subtentorial or basal cistern block ", since no clinical or other evidence is presented to suggest that success was in fact achieved in a single case treated by the author. However, the incidence and importance of spinal and other blocks would appear to have been greatly diminished by the introduction of combined treatment with streptomycin, PAS, and isoniazid.] *J. Lorber*

64. Tuberculous Meningitis Treated with A.C.T.H. and Isoniazid. A Comparison with Intrathecal Streptomycin

W. C. M. BULKELEY. *British Medical Journal* [*Brit. med. J.*] **2**, 1127–1129, Nov. 21, 1953. 4 refs.

Corticotrophin (ACTH) was given to 31 patients with tuberculous meningitis at the King George V Hospital, Durban, South Africa, as an adjunct to treatment with various combinations of streptomycin by intramuscular injection and isoniazid and PAS by mouth; 8 of the patients also received intrathecal injections of streptomycin [10 according to Table III]. A dose of 6 to 25 units of corticotrophin was given 6-hourly by intramuscular or subcutaneous injection for 1 to 5 weeks. The results obtained in these 31 patients treated during the period March, 1952, to March, 1953, were compared with those obtained in a series of 31 patients treated between March, 1950, and February, 1952, with very prolonged courses of streptomycin by intrathecal and intramuscular injection, PAS by mouth and, if required, tuberculin intrathecally. Three patients in the first series also received short courses of corticotrophin [5 according to Table III]. It is claimed that better results were obtained in the second series than in the earlier one, the mortality rate being 6·45% compared with 10% in 1951 and 60% in 1950. It is also claimed that streptomycin by intrathecal injection is no longer necessary in the treatment of tuberculous meningitis.

[This was not a planned and concurrently arranged controlled study. The patients received a variety of treatments and it is impossible to disentangle the numerous

variable factors. The tables contradict the statements in the text. The low mortality figures given in the text do not include all deaths, because it was felt that some were not due to the meningitis itself. The actual mortality was 5 of 20 (25%) in the first series and 6 of 31 (20%) in the second series. It is, however, impossible to compare the mortality rates in the two series because the periods of observation were different. Most of the patients in the second series were still being treated, and all the 6 deaths in that series occurred among the first 18 patients who were observed longest. Of these 18, only 12 received ACTH with isoniazid and 4 were already dead. For these reasons the conclusions in this paper are not acceptable. The frequency of deafness in the first series is not surprising considering that " daily intrathecal streptomycin was given until the C.S.F. was normal for several months ".] *J. Lorber*

65. **Daily Oxytetracycline (Terramycin) and Intermittent Streptomycin in the Treatment of Pulmonary Tuberculosis. An Investigation of the Administration of Two Grams of Oxytetracycline Daily**

F. L. MILLER, J. H. SANDS, L. J. GREGORY, J. A. HIGHTOWER, O. L. WEISER, and C. W. TEMPEL. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **69**, 58–64, Jan., 1954. 2 refs.

In this study, reported from Fitzsimons Army Hospital, Denver, Colorado, the results of treating 20 male patients suffering from advanced or moderately advanced pulmonary tuberculosis with 2 g. of oxytetracycline (" terramycin ") orally daily supplemented by 2 g. of streptomycin intramuscularly every third day for 120 days were assessed by a panel of five physicians and compared with the results of an earlier study made in the same hospital, in which 66 patients had received oxytetracycline in daily doses of 5 g. In 15 of the 20 cases the disease was predominately exudative and caseous; all 20 patients were sputum-positive, in 19 cavities were present, and none had received previous antituberculous drug therapy.

Clinically, 8 patients showed improvement of cough and 8 a significant reduction in sputum volume, while in 12 there was a gain in weight of over 5 lb. (2·3 kg.). All the patients showed radiological improvement, and 13 became sputum-negative for 3 months or longer (after the 120 days' treatment). One strain of bacillus was found to be resistant to streptomycin, but no resistance to oxytetracycline was encountered. About half of the 20 patients experienced some side-effects believed to be due to the oxytetracycline, the commonest being diarrhoea and pruritis ani; sore tongue was noted in 3 cases and cheilosis also in 3. In general, however, the reactions were transient and mild, and may have been associated with changes in the faecal microflora, notably the increase in the number of yeast-like fungi and *Proteus*, which were observed in the stools in half the cases.

The clinical and radiological improvement closely paralleled, although it was slightly less good than, that observed in patients in the earlier group receiving 5 g. of oxytetracycline daily, and was superior to that obtained by treatment with streptomycin alone. Undesirable reactions in the later group receiving the smaller dosage were milder, less persistent, and occurred in fewer patients, and the authors point out that no patient in this group lost weight, whereas 19·7% of those given 5 g. daily did so, probably because of the greater severity of gastrointestinal symptoms. The dose of 2 g. of oxytetracycline, however, did not give complete protection against the emergence of streptomycin-resistant tubercle bacilli. The authors conclude that the optimum dosage of oxytetracycline in conjunction with streptomycin is probably between 2 and 5 g. daily. *R. J. Matthews*

66. **Streptomycin and Oxytetracycline (Terramycin) in the Treatment of Pulmonary Tuberculosis**

E. ROTHSTEIN and M. JOHNSON. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **69**, 65–70, Jan., 1954. 12 refs.

In order to determine the effect of oxytetracycline (" terramycin ") upon the emergence of streptomycin-resistant tubercle bacilli the authors, working at the Veterans Administration Center, Dayton, Ohio, and the University of Cincinnati, analysed the results of 4 months' treatment with oxytetracycline and streptomycin of 81 tuberculous patients, 76 of whom had advanced or moderately advanced pulmonary disease. In all 81 cases streptomycin-susceptible bacilli were present at the start of treatment, and 17 patients were included because they had large cavities and might be expected to yield sputum which would be positive for *Mycobacterium tuberculosis* for at least 4 months. These 17 patients were given 5 g. of oxytetracycline daily by mouth and 1 g. of streptomycin intramuscularly twice weekly. The remaining 64 cases were unselected, except that they were all in need of chemotherapy and, like the others, had received no previous streptomycin therapy; these were given 1 g. of oxytetracycline daily with either 1 g. of streptomycin twice weekly (34 cases), or 2 g. once weekly (30 cases). When necessary, treatment was supplemented by the induction of pneumoperitoneum.

In assessing their results and comparing them with those in other reported series of cases, the authors consider that their findings of radiological improvement in 64 cases (80%), which was marked or moderate in 40 (50%), and sputum conversion in 34 cases (42%) do not differ materially from the results obtained by treatment with streptomycin and PAS. The toxicity of oxytetracycline in doses of 1 g. daily was insignificant, and the antibiotic was better tolerated than PAS. About one-fifth of the patients suffered from diarrhoea, which was more pronounced in those who received 5 g. daily. At the end of 4 months treatment, 3 of the patients had streptomycin-resistant strains of tubercle bacilli, and 42 had streptomycin-susceptible strains (the method of conducting the susceptibility tests is described in detail). The authors conclude that, for patients requiring streptomycin therapy but showing intolerance to PAS, 1 g. daily of oxytetracycline may be used as a substitute for the latter without increasing the risk of the emergence of streptomycin-resistant strains of tubercle bacillus—[a conclusion which appears to be justified].

R. J. Matthews

Venereal Diseases

67. **Treatment of Gonorrhoea with Two Grammes of Terramycin in Unequal Divided Doses over Twenty-four Hours**
R. R. WILLCOX. *Journal of the Royal Army Medical Corps* [*J. roy. Army med. Cps.*] **100**, 57–59, Jan., 1954. 4 refs.

Continuing his series of investigations of the effect of a 2-g. dose of oxytetracycline (" terramycin ") in the treatment of acute gonorrhoea, the author now reports from St. Mary's Hospital, London, the results obtained in 45 cases with an initial dose of 1 g. and 4 doses each of 250 mg. given at intervals during the following 24 hours. Of the 45 patients, 8 were not seen again after treatment. The remaining 37 were observed as follows: 35 for 4 to 7 days, 26 for 8 to 14 days, 22 for 15 to 18 days, and 14 for longer periods; the condition of 31 (83·8%) was satisfactory at the time the patient was seen; in one case treatment was a " definite failure ". Non-specific urethritis, which subsequently developed in 5 cases, was attributed to a double infection acquired at the same exposure, the incubation period of non-specific infection being much longer than that of gonorrhoea. The author notes the interesting fact that although oxytetracycline is claimed to be curative in established non-specific urethritis, it failed to act as a prophylactic in these cases. *Douglas J. Campbell*

68. **The Orally Administered Antibiotics in the Treatment of Nonspecific Urethritis. III. Oxytetracycline**
R. R. WILLCOX. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **4**, 173–177, Feb., 1954. 2 refs.

69. **Researches in Aetiology of Non-specific Urethritis**
R. R. WILLCOX. *British Medical Journal* [*Brit. med. J.*] **1**, 13–15, Jan. 2, 1954.

The author reports the results of a search for a possible bacterial or viral cause of non-specific urethritis. First, a comparison was made between the bacterial flora found in urethral cultures from 105 controls [nature not stated] and that in 81 urethral cultures taken from patients with urethritis before treatment and 69 taken after treatment with orally administered antibiotics. As little difference was found between the flora in the three groups, it was concluded that " bacterial urethritis " was not a common entity.

In skin tests carried out with antigens of members of the psittacosis–lymphogranuloma venereum group of viruses 17 urethritic patients and 11 controls gave negative results with psittacosis antigen; but 11 positive reactions were obtained with the antigen of lymphogranuloma venereum in 84 patients, compared with 3 in 62 control subjects. With the antigen of cat-scratch fever 2 positive reactions in 16 urethritic patients were observed, while 12 control patients all gave negative reactions. Complement-fixation tests with the antigen of lymphogranuloma venereum gave 6 positive results out of 141 samples of serum from patients, against 3 out of 132 control sera. Complement-fixation tests with the virus of enzootic abortion in ewes (thought to belong to the same group of viruses) gave 4 positive results in serum from 123 patients and 5 in serum from 127 controls.

Giemsa-stained smears of urethral scrapings from male patients were examined for inclusion bodies. Red- and blue-staining granules and granular " colonies " 1 to 6 μ in diameter were seen. An attempt was made to evaluate their significance by comparing their incidence in patients before treatment and after successful or unsuccessful treatment. The incidence of red granules and colonies was unaffected by treatment, suggesting that they were of no significance. Blue-staining granules and colonies, however, became fewer after successful treatment. Since they were also found in a proportion of urethral scrapings from patients with recently treated gonorrhoea, it was concluded that these bodies were merely products of inflammation. Attempts were also made to isolate a virus by inoculation of material into the lungs and brain of mice, into the conjunctiva, urethra, and knee-joint of baboons, subcutaneously into guinea-pigs, and into eggs by the chorio-allantoic route, but all failed to give any clear-cut evidence of an infective agent. *A. E. Wilkinson*

70. **The Observation of Serologic Response following Re-treatment for Seroresistance and Theoretical Considerations on the Meaning of Seroresistance**
G. R. CANNEFAX and E. B. JOHNWICK. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 18–23, Jan., 1954. 5 refs.

Failure of the serological reactions in cases of early latent syphilis to become negative after adequate treatment is commonly called " seroresistance ", and is defined here as " any degree of seropositivity 12 to 24 months following initial therapy ". Such a finding commonly leads to the administration of further treatment, and the authors have carried out investigations at the U.S. Public Health Service Medical Center, Hot Springs National Park, Arkansas, to determine the effectiveness of such treatment in bringing about the reversal of the serological findings.

A total of 135 patients were studied, each of whom had been treated for early latent syphilis with 3·75 mega units of penicillin, either as benzylpenicillin in peanut oil and beeswax (P.O.B.) or procaine benzylpenicillin in oil with 2% aluminium monostearate (P.A.M.). All were seroresistant after 12 to 24 months of observation, and at this stage 63 of them received further treatment with either 6·7 or 11·2 mega units of P.O.B. or P.A.M., those with the more strongly positive reactions receiving the higher dosage. The remaining 72 were left without further treatment, and observation and testing (with the

quantitative Kahn test) were continued for a further 12 to 24 months in all cases in both groups.

The average total diminution in strength of the Kahn reaction was somewhat greater in the control group than in the test group during the first 12 to 24 months of observation, but during the second period the average rate of fall in titre was much the same in both. Moreover, the rate of fall in those cases in which the titre at the end of the first period was high was the same as in those in which it was moderate or low, whereas during the first period the fall in titre was greatest in those cases with the highest initial titre. This suggests that the destruction or reduction of living treponemes or their antigenic products by penicillin contributed to the fall in titre during the first period, but not during the second, the initial treatment having eliminated the infection in both groups. The authors postulate that seroresistance is due to the persistence of immunological response after the termination of active infection, the reagin-producing mechanism continuing to function after the specific stimulus has been withdrawn. The longer the stimulus has been allowed to act, the greater the likelihood of such persistence occurring, as may be seen most strikingly in the finding of Hanchett and Perry (*J. vener. Dis. Inform.*, 1950, **31**, 277; *Abstracts of World Medicine*, 1951, **9**, 529) that 100% of patients with congenital syphilis treated under the age of 6 months and 86·5% of those treated before the age of 2 years became seronegative, whereas only 5·4% of those over the age of 2 at the time of treatment became seronegative. This theory would also explain the birth of non-syphilitic infants to seroresistant mothers who have received no treatment during pregnancy and the fact that the positive reaction often found in such infants at birth rapidly reverts to negative, the reagin not being produced by the foetal tissues, but being passively transferred from the mother through the placenta. *A. J. King*

71. Serologic Observations following Penicillin Treatment for Latent Syphilis

B. J. CHESTER, J. C. CUTLER, and E. V. PRICE. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 7–17, Jan., 1954. 4 figs.

The diagnosis of latent syphilis is based solely upon positive serological reactions in the blood, clinical signs being absent and the reactions of the cerebrospinal fluid being negative. The fact that the serological reactions do not become negative after treatment is not necessarily evidence of its failure, especially in cases of long standing, so that the evaluation of any form of treatment for latent syphilis demands the prolonged observation of many cases. The authors have analysed the records of 447 patients treated for latent syphilis with penicillin at the U.S. Public Health Service Hospital, Staten Island, New York, and observed for a period of 7 years in each case. At the time of treatment 172 of them were suffering from syphilis of less than 4 years' duration, which was the arbitrary definition of early latency; 205 had been infected for 4 or more years and were regarded as being in the stage of late latency; and in 70 cases the duration of infection could not be determined. Of the 447 patients, only 10 were women and 60% were white. Ages ranged from 17 to 72 years. The total amount of penicillin given varied, and the patients are divided into two groups according to whether they received less or more than 3·4 mega units. For patients with early infection the average total doses in the two groups were 1·5 and 3·8 mega units respectively, while the corresponding figures for those with late syphilis were 1·3 and 4·0 mega units; 76 patients received additional antisyphilitic treatment, some of them in the form of penicillin for non-syphilitic conditions and 53 of them for so-called failure of treatment. However, such additional treatment seemed to have had little effect on the serological reactions, which remained positive in 86% of the patients who received it.

No less than 5 routine qualitative serological tests were used—namely, the Mazzini, Kahn, Eagle, Hinton, and Kolmer tests—while quantitative tests were performed by the Mazzini and Kahn methods. Reactions became negative to the Kahn test more rapidly than to the other tests, and remained negative throughout the 7 years of observation in a higher proportion of cases. Six years after treatment the proportion of patients with early infections giving a negative response to the Kahn test was 53% compared with 34·5 to 39·0% with the other techniques, while 30·5% of those with late infections gave a negative response to the Kahn test and 9·7 to 16·9% to the other tests. In the quantitative tests the titre of the Mazzini reaction was consistently higher than that of the Kahn reaction, both before treatment and throughout the period of observation, though there was a tendency towards closer agreement between the two after treatment. Relatively few patients gave completely negative responses to all tests after treatment, but in the majority of cases the titres fell to 4 units or less. Patients with early latent syphilis usually gave more strongly positive reactions before treatment and showed a more rapid fall in titre after treatment than those with late latent syphilis. In general, however, the lower the titre before treatment, the more satisfactory the result. Comparison between the results obtained with the higher and lower dosages of penicillin showed that when response was measured by the Kahn or Mazzini tests the amount administered was not an important factor. According to the Hinton, Eagle, or Kolmer tests the administration of larger amounts of penicillin seemed to produce better results in early latent syphilis, but the difference was not statistically significant. There was no evidence of clinical progression or of the development of positive changes in the cerebrospinal fluid in any of these cases.

The authors consider that although observation after treatment had been perfunctory in some cases, the results of treatment with penicillin were favourable on the whole, and that the pattern of serological response described is the one to be expected after the successful treatment of patients with latent syphilis. *A. J. King*

72. Serologic Tests for Syphilis in Infectious Mononucleosis

C. J. D. ZARAFONETIS and J. F. KENT. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **43**, 253–258, Feb., 1954. 24 refs.

Tropical Medicine

73. **Onyalai. A Clinical and Laboratory Survey**
S. M. LEWIS and A. LURIE. *Journal of Tropical Medicine and Hygiene* [*J. trop. Med. Hyg.*] **56**, 281–289, Dec., 1953. 25 refs.

Onyalai is the African name for a fairly widespread purpuric disease characterized by sudden onset, spontaneous bleeding, haemorrhagic bullae mainly on mucous surfaces, marked thrombocytopenia, and prolonged bleeding time. At the African Institute for Medical Research, Johannesburg, and Pietersburg Hospital, Transvaal, the authors investigated 32 new cases of onyalai with a view to determining the specific defect in the coagulation mechanism. All the cases occurred in Africans (most of whom were Msutu) with the exception of one which occurred in a European from Southern Transvaal.

The cases fell into two groups, acute and chronic. Of the 21 acute cases, all but one showed clinical remission, with apparently complete recovery, within 2 months of onset of symptoms. Platelet counts determined later in 10 of these cases showed that the clinical remission was accompanied by a return of the count to a normal level. In the 11 chronic cases there was a history of previous episodes. In only 2 of these patients was the platelet count normal within 2 months of the onset of the observed acute symptoms, the remainder continuing to show thrombocytopenia. Although onyalai is reported to occur more frequently in males than in females, in the present series the sex distribution was nearly equal (17 males and 15 females). Symptoms consisted in headache and pain in the chest, abdomen, and elsewhere. Haemorrhagic bullae occurred on all parts of the mucous membrane of the oral cavity. Spontaneous bleeding occurred as epistaxis, haematuria, conjunctival haemorrhage, melaena, menorrhagia, and purpura of the skin, and in a high proportion of the female cases was related to the beginning of a menstrual cycle.

Laboratory investigation showed that thrombocytopenia was a constant finding; the bone-marrow picture was variable, only one case having a normal megakaryocyte count with platelet budding, while in 7 cases there was no platelet budding. A high megakaryocyte count was found in 12 cases, 8 of which had no platelet budding, and there was one case with a low megakaryocyte count. In 10 cases the eosinophil count was normal, but in 11 it was high. The coagulating mechanism was fully investigated in 5 cases, the detailed results being given in a table. The picture was one of prolonged bleeding time and increased capillary fragility in the presence of a markedly reduced platelet count, but no defect was observed other than that of prothrombin utilization of the kind seen in thrombocytopenic purpura and an associated defect in clot retraction. The best treatment at present remains blood transfusion. *R. Wien*

74. **Studies in Human Malaria. XXXI. Comparison of Primaquine, Isopentaquine, SN-3883, and Pamaquine as Curative Agents against Chesson Strain Vivax Malaria**
W. C. COOPER, A. V. MYATT, T. HERNANDEZ, G. M. JEFFERY, and G. R. COATNEY. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] **2**, 949–957, Nov., 1953. 2 figs., 7 refs.

In these further studies in human malaria, carried out under the auspices of the U.S. National Institutes of Health, Bethesda, Maryland, 204 volunteers, each infected with the Chesson strain of *Plasmodium vivax* by 10 mosquito bites, were divided into 6 equal groups and given 14-day courses of treatment starting on the 3rd to 5th day of patent parasitaemia. One of 4 different 8-aminoquinolines (2 in alternative doses) was administered to each group 6-hourly for 14 days in combination with quinine sulphate, the daily doses (all as base) being, primaquine 20 mg. or 10 mg., isopentaquine 60 mg., " SN-3883 " [8-(4-aminobutylamino)-6-methoxyquinoline] 60 mg. or 30 mg., pamaquine 60 mg., together with quinine 1 g.

It was found that the courses of SN-3883 (60 mg.) and primaquine (20 mg.) were the most effective in preventing relapse, the incidence of relapse being 9% and 15% respectively, compared with an incidence with the other courses of: SN-3883 (30 mg.), 21%; isopentaquine, 35%; primaquine (10 mg.), 65%; and pamaquine, 82%. Serious toxic effects were not observed with any of the compounds, and primaquine in a dose of 20 mg. per day was exceptionally well tolerated.

A further study undertaken to determine whether cure could be obtained by halving the treatment time (from 14 to 7 days) and giving the two most effective drugs in one dose daily showed that primaquine in a single dose of 30 mg. or 20 mg. daily, or SN-3883 in a dose of 60 mg. daily for 7 days, together with chloroquine 1·5 g. (base) for the first 3 days, was ineffective against the same severe infections, relapse incidence in these series being 90, 80, and 100% respectively. *I. M. Rollo*

75. **Relapse of Vivax Malaria Treated with Primaquine and Report of One Case of Cyanosis (Methemoglobinemia) due to Primaquine**
J. E. HANSEN, E. A. CLEVE, and F. W. PRUITT. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 9–12, Jan., 1954. 9 refs.

76. **An Investigation into Hyaluronidase as a Factor in the Mechanism of Tissue Invasion by *Endamoeba histolytica***
J. N. DELAMATER, J. B. MICHAELSON, F. A. HALLMAN, and H. BLUMENTHAL. *American Journal of Tropical Medicine and Hygiene* [*Amer. J. trop. Med. Hyg.*] **3**, 1–8, Jan., 1954. 13 refs.

Nutrition and Metabolism

77. **Water Intoxication. Differential Diagnosis of the Hypotonic Syndromes**
V. WYNN and C. G. ROB. *Lancet* [*Lancet*] **1**, 587–594, March 20, 1954. 34 refs.

The syndrome of water intoxication is discussed with reference to 24 cases seen at St. Mary's Hospital, London, 6 of which are described in some detail. Water intoxication is not uncommon postoperatively, but may be overlooked or confused with sodium depletion. It may be acute in onset or may develop gradually when the water intake is too high for several days after operation. It must be differentiated from " symptomless hypotonicity " and sodium depletion, the criteria for doing so being discussed. A serum sodium level of less than 120 mEq. per litre indicates water intoxication. There is no rigid distinction between the syndromes; indeed, depletion of base may in fact predispose to water intoxication. The absence of clinical dehydration is a significant feature in water intoxication, differentiating this condition from sodium depletion. In treatment the administration of hypertonic saline is safe and effectively controls all symptoms, including convulsions. *D. A. K. Black*

78. **The Metabolic Effects of Intravenous Administration of Calcium**
L. H. KYLE, M. SCHAAF, and L. A. ERDMAN. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **43**, 123–133, Jan., 1954. 6 figs., 13 refs.

The effect of intravenous administration of calcium by a standard infusion technique to patients with metabolic bone disease was studied at Georgetown University Hospital, Washington, D.C. For some days before the test the patient was given relatively constant amounts of calcium and phosphorus, the 24-hour collection of urine being analysed for calcium and phosphorus content. On the day of the test, and before food, the patient received over a 3-hour period an infusion of 500 ml. of isotonic saline containing approximately 10 mg. per kg. body weight of calcium gluconate. Water diuresis was maintained throughout the day, and at hourly intervals urine was collected and venous blood withdrawn for estimation of the calcium and phosphorus content. In healthy control subjects infusion of calcium was followed by a rise in the serum calcium and serum phosphorus levels which lasted several hours. There was an increase in the total urinary excretion of calcium and a decrease in that of phosphorus during the day of infusion. Healthy subjects retained approximately 60% of the infused calcium. A similar biochemical response was obtained in patients with osteoporosis and osteomalacia except that they retained more than 60% of the infused calcium. No such changes followed infusion of saline without calcium. In cases of increased or decreased parathyroid activity there was no rise in the serum phosphorus level and no decrease in urinary excretion of phosphorus in response to infusion of calcium. In one patient with primary renal disease and phosphate retention calcium infusion failed to increase the serum phosphorus level. *K. G. Lowe*

79. **Combined Beri-Beri and Wernicke's Syndrome with Epileptic Convulsions Observed among Korean Soldiers.** [In English]
F. BOM and K. Y. BOM. *Acta psychiatrica et neurologica Scandinavica* [*Acta psychiat. neurol. scand.*] **28**, 97–104, 1953. 8 refs.

During the winter of 1951–2, five cases of severe deficiency of thiamine were admitted to the Danish hospital ship *Jutlandia* while in Korean waters. The patients were all Korean soldiers, aged 21 to 26, who had been subsisting for some months on a diet low in thiamine and relatively high in carbohydrate content; dysentery and physical strain were predisposing factors. Brief case reports are given. Oedema and cardiac disorders were present in all and peripheral neuropathy in at least 4 cases, while a concomitant Wernicke's encephalopathy is held to account for the mental derangement and epileptiform convulsions which occurred in every case, having previously been described as occurring in Wernicke's encephalopathy by de Wardener and Lennox (*Lancet*, 1947, **1**, 11). There was slow recovery after administration of thiamine intravenously and other members of the vitamin-B complex [not specified] intramuscularly. There was some residual neuropathy.
H. M. Sinclair

80. **The Use of Fat Supplements in the Nutrition of Critically Ill Patients**
G. M. MINDRUM. *Journal of Clinical Nutrition* [*J. clin. Nutr.*] **1**, 503–512, Nov.–Dec., 1953. 3 figs., 22 refs.

The effect of a high-calorie, high-fat diet on patients who were critically ill was investigated at the Cincinnati General Hospital, Ohio. An emulsion containing fat (peanut, coconut, or olive oil) 50%, carbohydrate 15%, dried skimmed milk 23%, an emulsifying agent, and water to 100 ml. was given to 9 selected patients suffering from severe trauma, burns, empyema, carcinoma, or tuberculosis. It was administered by mouth or stomach tube in 100-ml. doses (510 Calories) after the ordinary meal from 3 to 6 times a day. All the patients had been steadily losing weight for three weeks or more and were generally deteriorating. None experienced any noteworthy ill effect from the emulsion and all gained weight rapidly. The improvement was marked by a sense of well-being, increased resistance to infection, and acceleration in the rate of wound healing. The author does not state the number of patients who were unable to tolerate the emulsion, but admits that some refused it. Of a group of nurses who wished to gain weight, 30% had to discontinue the emulsion because of anorexia, nausea, and diarrhoea. *H. E. Magee*

Gastroenterology

81. **Smooth-muscle Tumours of the Esophagus**
J. B. JOHNSTON, O. T. CLAGETT, and J. R. MCDONALD. *Thorax* [*Thorax*] **8**, 251–265, Dec., 1953. 4 figs., 47 refs.

In this paper from the Mayo Clinic the authors describe 21 cases of leiomyoma and 5 of leiomyosarcoma of the oesophagus selected from the surgical records of the clinic, and note that only 116 cases of the former and 13 of the latter have previously been reported in the literature. These tumours are over 120 times rarer than carcinoma of the oesophagus, and leiomyosarcoma constitutes only some 14% of all oesophageal sarcomata.

Leiomyoma is 3 or 4 times more frequent in the male than in the female, and in most cases occurs when the patient is between 20 and 50 years of age. Leiomyosarcoma, on the other hand, has nearly always been found to develop after the age of 50. The benign lesion is often asymptomatic, and when dysphagia does occur it tends to be mild and only very slowly progressive. In the sarcomatous form, however, dysphagia is the rule and is usually of short duration. Unlike leiomyomata elsewhere in the bowel, those in the oesophagus seldom, if ever, bleed or ulcerate; leiomyosarcoma on the other hand may do both. Leiomyomata may involve the stomach as well as the oesophagus and they are occasionally multiple.

The benign tumour can usually be enucleated and a cure thus effected, although extension into the stomach has on occasion made resection necessary. Of the 5 cases of leiomyosarcoma described, 4 were polypoid. Two were treated by oesophago-gastric resection and both patients are still alive, 6 years and 7 years respectively after operation. *H. Daintree Johnson*

STOMACH AND DUODENUM

82. **Further Studies on the Reduction of Gastric Acidity**
A. H. DOUTHWAITE and M. G. THORNE. *British Medical Journal* [*Brit. med. J.*] **1**, 183–184, Jan. 23, 1954. 1 fig., 1 ref.

It was reported by Douthwaite and Batty Shaw (*Brit. med. J.*, 1952, **2**, 180; *Abstracts of World Medicine*, 1953, **13**, 30) that the gastric acidity of patients with duodenal ulcers was more effectively reduced by the continuous sucking of alkaline tablets than by the intermittent administration of antacids. These findings were open to criticism in that they were based on measurement of the *p*H of a relatively inert gruel meal, and the investigation has therefore been repeated on 12 patients with peptic ulcer taking ordinary meals, except that solid foods were minced in all but 2 cases. The ulcer in one case was in the stomach and in 11 in the duodenum. The patients were deprived of all drugs for 18 hours before the test, which was started within an hour of taking their usual breakfast or lunch, 2-ml. samples being drawn from the gastric contents every 15 minutes and the *p*H measured electrometrically. During the first hour no medicaments were given, but in the subsequent 2 hours the patients sucked either alkaline tablets or dummy tablets without alkali, the test being repeated the next day with the other type of tablet. The alkaline (" nulacin ") tablets consisted of solids from whole milk combined with dextrins and maltose, together with magnesium trisilicate, magnesium oxide, calcium carbonate, and magnesium carbonate. Lodged between the gum and cheek, the tablet was found to take 20 to 30 minutes to dissolve.

In every case the alkaline tablets produced a considerable lowering of the acidity of the gastric contents, whereas the dummy tablets had little or no effect. But although it is generally accepted that reduction of the acidity of the gastric contents is desirable in the treatment of patients with peptic ulcer, the optimum degree of neutralization is less easy to determine. To maintain the *p*H of the stomach contents at the same level as that of the plasma —namely, 7·4—might encourage bacterial growth, and the authors suggest arbitrarily that " an acidity corresponding to 1 clinical unit represents satisfactory neutralization ". They found that *in vitro* one of the alkaline tablets used neutralized about 90 ml. of N/10 hydrochloric acid; *in vivo* the food contributes to the reduction of acidity, so that one tablet an hour may be effective. No alkalosis will occur provided the daily dose does not exceed 15 tablets. It is claimed not only that the sucking of alkaline tablets will relieve the symptoms of duodenal ulcer, but also that their regular use in the symptom-free patient seems to reduce the tendency to relapse. *E. Forrai*

83. **Chronic Superficial Gastritis: Observations on Clinical and Histopathologic Significance**
E. D. PALMER. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **20**, 369–372, Dec., 1953. 2 figs., 3 refs.

Chronic superficial gastritis was present in 83 out of 2,500 patients examined gastroscopically at the Walter Reed Army Hospital, Washington, D.C. In 62 of these patients some other gastrointestinal or general disease (including duodenal ulcer in 22 cases and gastric ulcer in 9) was present as well. In the remaining 21 patients the gastritis was judged to be responsible for the gastrointestinal symptoms. Gastric haemorrhage occurred in 16 of these 21 patients; in 9 no possible source other than the superficial gastritis was found, and in 3 the haemorrhage was the first and only symptom.

Serial gastroscopic examinations showed generalized gastritis with a mucous exudate and hyperaemia in most cases, and erosions in one-third. There was an appreciable change in the severity of the disease after one week's treatment in some cases, but in most a month or more was

required. In a few the condition remained static for long periods. In 11 instances gastroscopic examination during active haemorrhage following ice-water lavage revealed that the haemorrhage originated from multiple gastric erosions. Chronic atrophic gastritis developed in one patient who was followed up for 5 years, although the gastric mucosa had been normal during hospital treatment. In 13 cases histological examination of biopsy specimens of the diseased gastric mucosa, taken by the vacuum-tube technique, indicated that the most significant change was necrobiosis of the cells at the neck of the glands.

The author concludes that the pathological process which causes chronic superficial gastritis leads to the spontaneous development of multiple mucosal erosions, and when this occurs throughout the mucosa sudden haemorrhage may result. *Joseph Parness*

84. **A Study of the Age Curve for Cancer of the Stomach in Connection with a Theory of the Cancer Producing Mechanism**
P. STOCKS. *British Journal of Cancer* [*Brit. J. Cancer*] **7**, 407–417, Dec., 1953. 3 figs., 3 refs.

Death rates from cancer of the stomach in 5-year periods from 1921 to 1950 in England and Wales, taken from the Registrar-General's statistics for males and females in quinquennial age groups, show that during the last 20 years there has been a slight decline in the mortality from this cause among males and a more marked decline among females aged between 25 and 75. Death from cancer of the stomach before 15 years of age was a great rarity, but the mean rate in each age group for the whole period rose steadily from the age of 15 to 80 years.

Assuming (1) that cancer of the stomach will develop after c "encounters" with the causative substance or influence (an "encounter" being the amount of exposure taking place in 1 year); (2) that the average risk for an individual of an encounter occurring in 1 year is q, and that $p=1-q$; and (3) that Ny_a is the number of persons becoming affected on reaching the age a out of N born, assuming none to die before being affected, then

$$Ny_a=\frac{N(a-1)(a-2)\ldots c}{1\,.\,2\ldots(a-c)}\,p^{a-c}q^c$$

If N is one million, this formula gives the rate per million living at which a cohort becomes affected by the cancerous process in a year at age a. Satisfactory agreement with the observed data was obtained for values $c=5$ and $q=0{\cdot}033$ for males and $0{\cdot}027$ for females. For other values of c no satisfactory fit could be obtained for any value of q. There was a lag of about 18 years between exposure and death from cancer. The death rate from cancer of the stomach is higher in urban than rural areas, the relative excess being greater at younger ages; this excess could be accounted for by assuming a slightly higher value for q (that is, a slightly higher risk in towns at all ages) without altering c.

This theory is not incompatible with the theory of multiple mutations (Nordling, *Brit. J. Cancer*, 1953, **7**, 68) if the number of mutations necessary for the development of cancer is taken as 5, and if the gene mutations are assumed to be caused by the "encounters" defined above. *M. Lubran*

85. **Banthine in the Treatment of Peptic Ulcer**
P. BECHGAARD, H. O. BANG, A. L. NIELSEN, and E. TOBIASSEN. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **21**, 38–41, Feb., 1954. 9 refs.

The literature on "banthine" [methantheline] therapy is surveyed and our own results are reported. A series of 34 patients suffering from roentgenographically demonstrable chronic peptic ulcer, which had persisted for at least 2 years, was treated with banthine, 50 mg. 4 times a day for one year. After the lapse of one year one-third of the patients were free from pain, and in one-fifth no ulcer could be demonstrated radiologically. Ten of the patients had been subjected to operation. In another therapeutic experiment 134 ulcer patients were treated for 3 months, 68 with banthine 50 mg. 4 times a day, and 66 with placebo. All were treated as out-patients after a stay of about 3 weeks in the hospital. Of those patients treated with banthine, 65% were improved or cured clinically as compared with 56% of those treated with the placebo. Radiologically the results were 23% and 13% cured respectively.

It is concluded that banthine has a symptomatic effect and may be a good supplement to the conventional ulcer therapy, but that banthine alone exerts no distinct curative effect in peptic ulcer.—[Authors' summary.]

LIVER

86. **Thrombosis of the Portal Vein in Cirrhosis Hepatis**
A. H. HUNT and B. R. WHITTARD. *Lancet* [*Lancet*] **1**, 281–284, Feb. 6, 1954. 3 figs., 7 refs.

In reporting 7 cases of thrombosis of the portal vein in patients suffering from cirrhosis of the liver, the authors state that this complication has not yet been placed in perspective in relation to change in the clinical course of the disease, and particularly in relation to oesophageal haemorrhage, ascites, coma, and sudden unexpected deterioration in the state of the patient.

The 7 cases were observed at St. Bartholomew's Hospital, London, among 134 in which a diagnosis of portal hypertension had been made [but we are not told on what this diagnosis was based when the cause was not hepatic cirrhosis]. Apart from those cases diagnosed at operation, thrombosis of the portal vein may be suggested by a good portal phlebogram, but it is pointed out that appearances need to be interpreted with caution.

It is shown that the presence of extensive thrombosis does not exclude a successful shunt operation, provided the thrombosis is recent and the thrombus removed with care. The use of heparin in such cases is discussed.
J. W. McNee

87. **The Liver in Extrahepatic Biliary Obstruction**
C. M. LEEVY, C. K. DVORSCHAK, and A. M. GNASSI. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 272–278, March, 1954. 1 fig., 21 refs.

88. **The Liver as a Site and Source of Cancer**
G. R. CAMERON. *British Medical Journal* [*Brit. med. J.*] **1**, 347–352, Feb. 13, 1954. Bibliography.

The fact that the liver becomes involved in the secondary spread of carcinoma in a high proportion of cases is known to all. Many assume, without thinking further, that the reason for this must be quite simple and not really worth pondering about. But except from tumours in the intestinal tract, from which venous blood passes directly to the liver by the portal vein, emboli must pass through the lungs to get to the liver. Why then are metastases so much more common in the liver than in the lungs in, say, cancer of the breast?

The author considers this and many cognate matters concerning the mode of spread of cancer and the difficult problem of the suitability of the " soil " or environment for the development of metastases, especially in the liver. He concludes on the stimulating and optimistic note that we must not be deterred from searching for means of circumventing the spread of cancer, even to the liver, even before we know the cause of primary cancer.

[This very thoughtful paper, which exhibits the now well-known philosophical outlook of the author, is well worth careful study in the original by physicians, surgeons, and pathologists.] *J. W. McNee*

INTESTINES

89. **The Effect of ACTH Therapy upon the Course of Chronic Ulcerative Colitis**
E. D. KIEFER and J. M. ELLIOTT. *Gastroenterology* [*Gastroenterology*] **26**, 29–31, Jan., 1954. 1 ref.

ACTH was given to 35 patients with chronic ulcerative colitis at the Lahey Clinic, Boston, and in this paper the authors report their findings after an observation period of 2 years. The patients were divided according to the clinical condition into 5 groups, and the results are reported for each group. Group 1 included 8 patients with severe and extensive destruction of the colon associated with severe systemic symptoms. There was temporary improvement in 6 of the patients which rendered an emergency operation unnecessary, but eventually ileostomy had to be performed on all 8 patients. One patient died after discharge from hospital. Group 2 contained 5 patients with advanced organic changes and chronic debility and diarrhoea; they were, however, in a state of remission. Follow-up examination revealed that the condition was unchanged in 4, and that the fifth patient, a boy of 14, had been in good remission for 2 years. Group 3 included 8 patients with long-standing colitis but with limited and less severe organic changes in the colon. Of these, 7 responded to the initial treatment, but 5 of the 7 subsequently relapsed, 2 of them requiring ileostomy and colectomy. Group 4 contained 8 patients with active colitis of short duration and severe systemic symptoms. Of these, 5 improved with the initial treatment, 2 of them being well at the time of the follow-up examination. Group 5 contained 6 patients with limited colitis or proctitis but no systemic symptoms. Three of these had done well, but the remaining 3 were worse.

The authors conclude that " ACTH does not replace any of the established medical or surgical measures in the treatment of ulcerative colitis but . . . has an important place in the management of selected cases ".
H. F. Reichenfeld

90. **The Development of Cancer in Chronic Ulcerative Colitis**
J. A. BARGEN, W. G. SAUER, W. P. SLOAN, and R. P. GAGE. *Gastroenterology* [*Gastroenterology*] **26**, 32–37, Jan., 1954. 1 fig., 4 refs.

To determine the incidence of carcinoma of the bowel in patients with chronic ulcerative colitis the authors reviewed the case histories of 2,000 patients who were first seen at the Mayo Clinic between Jan. 1, 1918, and Dec. 31, 1937. Of these, 1,564 were selected for investigation because they were under 50 when ulcerative colitis was first diagnosed, were followed up for at least a year after the diagnosis was made, and were free from malignant disease for at least a year.

It was found that 98 of these patients had developed cancer of the rectum or colon, the disease being fatal in all of them. Malignant disease was diagnosed at the Mayo Clinic in 43 cases and elsewhere in 33, being verified at necropsy on 11 and at operation in 14 of the latter group. In the remaining 22 cases reliable information was obtained from the relatives.

The death rate from cancer of the colon or rectum among these patients was compared with the expected death rate from the same cause among the general population, as calculated from *United States Vital Statistics, Special Reports*, 1949. This showed that cancer of the lower bowel was 20 to 30 times more frequent among patients with chronic ulcerative colitis than among the general population. In the U.S.A. the annual death rate from carcinoma of the colon among patients with ulcerative colitis is estimated to be between 1 and 2%. *H. F. Reichenfeld*

91. **The Association of Peptic Ulcer with Chronic Ulcerative Colitis**
J. A. HALSTED, E. T. YUHL, L. A. STIRRETT, and W. F. BARKER. *Gastroenterology* [*Gastroenterology*] **26**, 65–69, Jan., 1954. 12 refs.

Among 40 consecutive cases of chronic ulcerative colitis seen at the University of California Medical Center, Los Angeles, between July 1, 1950, and Jan. 1, 1953, there were 5 cases of coexistent duodenal ulcer. These 5 are described in detail in the present paper.

The patients were men between 24 and 60 years of age. In 3 the symptoms of duodenal ulcer antedated the onset of the colitis by 2 to 17 years, and in 2 the colitis was present for several years before the duodenal ulcer developed. The diagnoses of colitis and ulcer were confirmed by sigmoidoscopy and radiography. One patient, in whom the duodenal ulcer was apparently inactive, also had ankylosing spondylitis. After 4 weeks' treatment with cortisone and ACTH symptoms of low-grade intra-abdominal inflammation developed, which were found to be due to perforation of the duodenal ulcer.
H. F. Reichenfeld

Cardiovascular System

92. **Cardiac Surgery under Hypothermia**
C. P. BAILEY, B. A. COOKSON, D. F. DOWNING, and W. B. NEPTUNE. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **27**, 73–95, Jan., 1954. 14 figs., 21 refs.

In this paper from the Hahnemann Medical College and Hospital and the C. P. Bailey Thoracic Clinic, Philadelphia, the authors discuss the rationale of hypothermia, stating that at low temperatures the demands of the body for oxygen are small and that myocardial activity is depressed. They describe briefly the experimental work which has been done on the problem of "cooling", and stress the risk of air embolism when the left side of the heart has been opened.

They then discuss the indications for hypothermia in cardiac surgery, giving it as their opinion that it is preferable to any heart–lung apparatus which has so far been devised. They consider that only by use of cooling can large inter-atrial septal defects be properly repaired, and narrate some of their experiences with hypothermia in this condition. In describing some of the many methods by which hypothermia can be produced they state that they consider the procedure has only a limited application—apart from inter-atrial septal defects, cooling is called for only in the case of infants with a severe degree of congenital cyanosis where a prolonged interruption of the blood supply to the vital centres may be necessary and as a means of permitting open surgery on the right side of the heart. The contraindications to hypothermia are listed as: severe myocardial damage, acquired heart disease, and left-sided lesions requiring an open technique. *J. R. Belcher*

93. **Cardiac Output: a Clinical Comparison of the Direct Fick, Dye, and Ballistocardiographic Methods**
W. A. NEELY, F. C. WILSON, J. P. MILNOR, J. D. HARDY, and H. WILSON. *Surgery* [*Surgery*] **35**, 22–29, Jan., 1954. 1 fig., 13 refs.

A comparative study of various methods for the determination of cardiac output, undertaken at the Medical College of the University of Tennessee, is described. The direct Fick and ballistocardiographic methods are critically reviewed and their disadvantages pointed out: thus the former method requires intracardiac catheterization, while the latter is not applicable to very ill patients. The dye method is more easily performed than either of the above, and is readily applicable clinically.

All three methods were compared in experiments on 11 normal subjects, and the direct Fick and dye methods in experiments on 22 normal subjects. The ballistocardiographic method gave consistently good results and was much the most easily performed, but its use is virtually limited to the healthy subject. The accuracy of the Fick method appeared to be no greater than that of the dye method, the standard deviation being approximately 2·0 (30%) in each case. Multiple measurements with any of the three methods, performed on the same subject at the same time, agreed to within approximately 10%. *A. I. Suchett-Kaye*

94. **Workshop Experience with the "Disabled" Cardiac**
A. JEZER, B. S. BLACK, C. BENNEY, F. HASELKORN, G. AUERHAN, H. L. CHRYSTALL, R. ATKINSON, and D. ADELSON. *British Journal of Physical Medicine* [*Brit. J. phys. Med.*] **17**, 8–12 and 24, Jan., 1954. 2 figs., 10 refs.

The authors recount their experiences with 144 patients with severe cardiac disease admitted to the Altro Workshops, New York, for rehabilitation. It was found that by adopting a daily routine of two 2-hourly work schedules with a midday rest, gradually augmenting this, at intervals of several weeks, by half an hour each day, a full 7- to 8-hour working day could be attained. For patients who maintained this for some weeks without detriment a job was found in industry. A total of 54 patients were successfully rehabilitated, and these obtained outside employment within one year of starting their training. The high death rate (18, or 12·5%) in this small series emphasizes that the sample was chosen from seriously ill patients. The factors responsible for failure of rehabilitation were: (1) advancing cardiac failure or angina, and (2) emotional complications, in about equal proportions. Integration of case worker, cardiologist, and psychiatrist proved an essential feature of successful rehabilitation. Only 12 to 15% of patients with cardiac infarction were disabled as a direct result of the heart lesion, suggesting that greater optimism in the capacity of these subjects for future employment could be justified. The electrocardiogram was not found to be a satisfactory index of work capacity. *J. L. Lovibond*

95. **Pulmonary Hypertension in Congestive Heart Failure Complicating Chronic Lung Disease**
W. WHITAKER. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **23**, 57–72, Jan., 1954. 9 figs., 17 refs.

The investigation described in this paper was undertaken at the Royal Hospital, Sheffield, to determine the relation between pulmonary arterial blood pressure and the right auricular pressure, the oxygen and carbon dioxide content of the blood, the cardiac output, and the haematocrit value in patients with chronic lung disease. All the 26 patients were free from associated ischaemic, rheumatic, or hypertensive heart disease, but 13 had congestive heart failure while 13 had none.

The pulmonary arterial pressure in patients without heart failure ranged from 8 to 33 mm. Hg, while that of patients in failure ranged from 37 to 59 mm. Hg. During recovery the pressure fell, frequently to normal. The highest pressure was recorded with the most severe degree

of anoxia in patients with heart failure, and the lowest with the least degree of anoxia in patients not in failure. The fall in pressure with recovery was always associated with an increase in both arterial and mixed venous blood oxygen saturation. Acutely induced anoxia caused a rise in pulmonary arterial pressure in 3 out of 4 patients; no change in pressure, however, was observed in the fourth patient, in whom there was no significant alteration in the blood oxygen saturation.

The CO_2 content of mixed venous blood was higher in patients with pulmonary hypertension and heart failure than it was in those with lower blood pressure and no history of heart failure. A fall in pulmonary arterial pressure with recovery was associated with a fall in the CO_2 content of mixed blood.

In this series of cases the cardiac output was usually normal, though in some cases it rose as pulmonary arterial pressure fell during recovery. Increase in blood viscosity did not appear to be an important cause of pulmonary hypertension, since recovery from failure was not always accompanied by a fall in the haematocrit value. The results of ventilation tests indicated that there was no direct correlation between impairment of ventilatory function and the development of congestive heart failure in chronic lung disease.

E. G. Rees

DIAGNOSTIC METHODS

96. **Electrocardiographic Changes in the Dumping Syndrome**

C. N. PULVERTAFT. *Lancet* [*Lancet*] **1**, 325–329, Feb. 13, 1954. 8 figs., 8 refs.

At the County Hospital, York, electrocardiograms were recorded before and after a standard meal from 33 patients who had undergone partial gastrectomy. Of these patients, 26 complained of the dumping syndrome. During the test 14 patients had symptoms of the dumping syndrome, and in all of these electrocardiographic changes were noted—lowering or flattening of the T wave, usually associated with an exaggerated U wave, and occasionally sagging of the S–T segment and inversion of the T wave—together with an increase in the heart rate. Of the 12 patients with the dumping syndrome who did not experience symptoms during the test, one showed flattening and 5 showed slight lowering of the T wave, while 9 showed an increase in heart rate of at least 10 beats a minute. The remaining 7 patients had never had symptoms of the dumping syndrome, and none of these showed any electrocardiographic changes, though in 2 cases the heart rate increased by about 10 beats a minute. No fall was noted in the serum potassium level, which was determined in 13 cases before and again 15 to 25 minutes and 35 to 45 minutes after the meal (that is, at the times of onset and subsidence of symptoms). The electrocardiographic changes and symptoms could be induced by giving glucose in hypertonic solution or as powder, but not by giving calcium caseinate, and it is suggested that the vasomotor aspects of the dumping syndrome are caused by the excessively rapid absorption of sugar that follows partial gastrectomy. Although similar electrocardiographic changes can be produced by the subcutaneous or intravenous injection of adrenaline, no significant increase in urinary adrenaline content was found, despite the presence of severe symptoms, in the 2 cases in which it was determined, and the rise in blood adrenaline level following the ingestion of 100 g. of glucose was no greater than in normal subjects.

William A. R. Thomson

97. **Endocavitary Oscillography. Recording Technique and Study of Tracings from Normal Subjects and Patients with Heart Disease.** (Oscillographie endocavitaire. Technique d'enregistrement et étude morphologique chez les normaux et chez les cardiaques)

A. STRANO, F. TESTONI, and G. FILOCAMO. *Cardiologia* [*Cardiologia* (*Basel*)] **24**, 15–39, 1954. 34 figs., 12 refs.

The authors present a comprehensively illustrated study of intracavitary oscillographic pressure-tracings recorded at the University Institute of Medical Pathology, Rome, from over 200 normal subjects and patients with various cardiac conditions. The technique, which is described in detail, consists in the use of a radio-opaque cardiac catheter bearing at its distal end a small rubber bulb and communicating proximally, via metal tubing, with an optical system containing a Franck's oscillographic capsule; through this apparatus pressure changes are recorded simultaneously with the electrocardiogram and phonocardiogram.

The authors demonstrate that this system provides a more accurate and more detailed tracing than a simple manometric record, particularly for intra-auricular readings, and that by its use waves due to mechanical faults are eliminated, clear records of even slight pressure changes are obtained, and the tracings show a constant pattern, apart from respiratory modifications or factors external to the recording system. Thus it is possible to define accurately the chronological relations between changes in endocavitary pressures and the electrical and auscultatory findings, so permitting exact calculation of the duration of the phases of the cardiac cycle.

The auricular oscillogram in normal subjects showed three principal waves: presystolic, systolic, and diastolic. These waves are analysed in detail and related to simultaneous electrocardiographic, respiratory, pulse, or manometric tracings. The oscillographic changes observed in cases of auriculo-ventricular block, tricuspid incompetence, fibrillation, and constrictive pericarditis are discussed and illustrated. Tracings from the right ventricle of normal subjects are also described, and compared with those obtained from patients with tachycardia, extrasystoles, and constrictive pericarditis, in which characteristic changes appear. Oscillograms from the pulmonary artery differ little from manometric tracings.

R. S. Stevens

98. **A New Synthesis of Some of the Physical Foundations of Clinical Electrocardiography**

R. H. KESSELMAN. *American Heart Journal* [*Amer. Heart J.*] **47**, 360–368, March, 1954. 6 figs., 13 refs.

CONGENITAL HEART DISEASE

99. Pulmonary Hypertension in Congenital Heart Disease

H. J. C. SWAN, J. ZAPATA-DIAZ, H. B. BURCHELL, and E. H. WOOD. *American Journal of Medicine* [*Amer. J. Med.*] **16**, 12–22, Jan., 1954. 4 figs., 42 refs.

The pulmonary arterial blood pressure was studied in relation to flow in (1) 24 cases of isolated atrial septal defect, (2) 20 of ventricular septal defect, and (3) 24 of patent ductus arteriosus at the Mayo Clinic. Pulmonary hypertension (defined as a mean pulmonary arterial pressure of more than 40 mm. Hg.) occurred in 4 of the 24 patients in Group 1, in 18 of the 20 in Group 2, and in 13 of the 24 in Group 3. The pulmonary blood flow (expressed in relation to surface area) was on the other hand much the same in all three groups, the average being about double the systemic flow.

No explanation was found for the higher incidence of a raised pulmonary vascular resistance in Groups 2 and 3 than in Group 1, but it is pointed out that with a lower resistance the shunt would have been much greater when the defect was at arterial or ventricular level. It is again suggested that the increased resistance may be due, in part at least, to persistence of the foetal structure in the small pulmonary arteries and arterioles.

Paul Wood

100. Pulmonary Valvuloplasty under Direct Vision Using the Mechanical Heart for a Complete By-pass of the Right Heart in a Patient with Congenital Pulmonary Stenosis

F. D. DODRILL, E. HILL, R. A. GERISCH, and A. JOHNSON. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **26**, 584–597, Dec., 1953. 12 figs., 5 refs.

The authors describe the treatment of a case of pure pulmonary stenosis at the Harper Hospital, Detroit, by open operation, during which a mechanical heart was used. The patient was a 16-year-old male with shortness of breath, but with no cyanosis, clubbing of the fingers, or polycythaemia. A transverse incision dividing the sternum and opening both pleural cavities was used. A cannula was placed in the pulmonary artery to the right lower lobe and another into the right atrium. The mechanical heart which has previously been described by the authors (*J. thorac. Surg.*, 1952, **24**, 134) was then attached and the right-heart circulation deflected from the ventricle, heparin being used to prevent clotting. The pulmonary artery (greatly enlarged) was freed from the aorta and clamped distally. Another clamp was then applied to the pulmonary conus and the vessel incised so as to expose the cone-shaped valve. This was cut and portions excised so as to make a bicuspid valve, after which the incision in the pulmonary artery was sutured, the mechanical heart was slowly shut off, and the cannulae removed. The patient made a satisfactory recovery.

The authors claim that this is the first time that the right heart has been completely and successfully by-passed. It is pointed out, however, that the method could not be used in cases of Fallot's tetralogy or of any other condition in which the two sides of the heart are in communication.

[It is not clear what objections there were to performing a transventricular "blind" valvotomy in this case. The advantages of an open valvuloplasty have to be balanced against the risks of the more complicated operation using a mechanical heart.]

T. Holmes Sellors

101. Pulmonary Valvulotomy. Results of Operation in Twenty-five Cases

G. H. HUMPHREYS, S. POWERS, H. FITZPATRICK, and B. M. LANMAN. *Surgery* [*Surgery*] **35**, 9–21, Jan., 1954. 7 figs., 14 refs.

The authors report their experience in 25 cases of pulmonary valvotomy performed at the Columbia-Presbyterian Medical Center, New York, during the period 1950–2 by the Brock technique. The youngest patient was 4 months and the oldest 24 years old, 12 being aged between 6 and 10 years. Investigations performed included venous catheterization, direct cardiac catheterization immediately before and after valvotomy, and studies with radioactive isotopes to determine the direction and degree of intracardiac shunt, but these were not all carried out in every case.

A pure valvular stenosis, without a septal defect, was present in 9 cases. In all but one of these there was a marked clinical improvement after operation, and right ventricular pressure tracings in 6 showed a change from a low damped curve to one with a characteristic dicrotic notch, demonstrating the restoration to proper function of the pulmonary valve. Valvular stenosis with an auricular septal defect was present in 5 cases; clinical results were "excellent" in 2, "good" in 2, and "questionable" in one case. The value of taking pressure tracings at the time of operation was shown in one patient in whom an adequate fall in right ventricular pressure was obtained only after the second dilatation. Valvular stenosis with a ventricular septal defect was present in 11 cases. In this group the right ventricular pressure was the same as, or less than, the aortic pressure, whereas in the two previous groups the former pressure was frequently the greater. Also in this group there was a less striking fall in ventricular pressure after valvotomy, and the clinical improvement was rather variable and often disappointing.

R. L. Hurt

102. Congenital Mitral Stenosis

C. FERENCZ, A. L. JOHNSON, and F. W. WIGLESWORTH. *Circulation* [*Circulation* (*N.Y.*)] **9**, 161–179, Feb., 1954. 4 figs., 42 refs.

In this paper from the Children's Memorial Hospital (McGill University), Montreal, 9 cases of congenital mitral stenosis found at necropsy since 1939 are recorded. All had associated abnormalities, chiefly patency of the ductus arteriosus and aortic stenosis; in one case there was a ventricular septal defect with an overriding aorta. The age of the children at death ranged from 3 weeks to 2 years. In no case was mitral stenosis diagnosed

clinically, although in one it was suspected on account of delayed emptying of an enlarged left auricle seen in the angiocardiogram. Most of the cases presented with congestive failure and pulmonary oedema of sudden onset. A transient mitral diastolic murmur was noted in one case. The electrocardiogram showed right ventricular hypertrophy in all 5 cases in which it was taken, even though there were associated left-sided lesions.

Congenital mitral stenosis is probably more frequent than has been thought. A search of the literature since 1846 revealed 34 reported cases, in 8 of which the mitral stenosis was an isolated abnormality. These included 2 cases reported from Birmingham in which the diagnosis was made clinically and valvotomy performed, successfully in one case. The fact that of the 43 patients concerned all but one died under 3 years of age testifies to the severe consequences of this malformation.

C. W. C. Bain

CHRONIC VALVULAR DISEASE

103. **The Effect of Lanatoside C on the Circulatory and Ventilatory Changes of Chronic Rheumatic Heart Disease with Mitral Stenosis**

F. D. GRAY and F. G. GRAY. *American Heart Journal* [*Amer. Heart J.*] **47**, 282–296, Feb., 1954. 1 fig., 28 refs.

Lanatoside C has been shown to produce both beneficial and deleterious effects, sometimes in the same patient, in cases of chronic pulmonary disease. In this further study of the drug carried out by the Cardiovascular Study Unit, Yale University, 6 patients suffering from chronic rheumatic heart disease with mitral stenosis were investigated by cardiac catheterization after an intravenous injection of 1·4 mg. of lanatoside C, digitalization being maintained by means of oral preparations. Pulmonary function was studied in all cases on the day before and again on the day after digitalization.

Clinical improvement was noted in only 3 of the 6 patients. Lanatoside C consistently increased cardiac output in 5 cases by increasing the right ventricular and peripheral arterial pressures and the rate of systemic blood flow. In the 6th case, in which the mitral stenosis was complicated by aortic stenosis and mitral regurgitation, there was no increased rate of systemic blood flow.

The practical application of effective digitalization with lanatoside C in the treatment of patients with rheumatic valvular heart disease or in the selection of cases of mitral stenosis for valvotomy is discussed.

A. I. Suchett-Kaye

104. **Clinical Diagnosis of Pulmonary Hypertension in Patients with Mitral Stenosis**

W. WHITAKER. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **23**, 105–112, Jan., 1954. 4 figs., 9 refs.

The author, working at the Royal and City General Hospitals, Sheffield, has examined 25 patients with mitral stenosis in an attempt to determine whether correlation was close enough between the mean pulmonary arterial blood pressure and the clinical, electrocardiographic, and radiological signs to make possible a clinical evaluation of the degree of pulmonary hypertension. Pulmonary arterial pressures were measured by cardiac catheterization. Pulmonary hypertension was arbitrarily classed as "mild" in 7 patients with mean pulmonary arterial pressures less than 40 mm. Hg, "moderate" in 10 patients with pressures between 40 and 69 mm. Hg, and "severe" in 8 in whom pressures ranged from 70 to 108 mm. Hg.

Results showed that whereas haemoptysis and nocturnal dyspnoea were more common in patients with moderate or severe pulmonary hypertension, little reliance could be placed on these symptoms alone in assessing the degree of hypertension. Prominent auricular waves in the jugular venous pulse were found to be a valuable sign of severe pulmonary hypertension in patients with sinus rhythm. The palpation of a systolic "lift" over the 2nd and 3rd left intercostal spaces was of little positive value in indicating the degree of pulmonary hypertension, since it was present in most of the patients in all three groups, but the finding of a palpable second heart sound was an important indication of severe or moderate pulmonary hypertension in patients with mitral stenosis.

A loud pulmonary second sound was to be heard in all but 2 of the patients and is considered to be an unreliable guide to the degree of pulmonary hypertension, but a loud second element of a duplicated second sound, heard in 3 of the severe and 4 of the moderate cases, is a definite, though inconstant, sign of severe or moderate pulmonary hypertension. A Graham Steell murmur was present in 7 of 8 patients with severe pulmonary hypertension, but owing to the difficulty of excluding aortic incompetence the value of this sign was considered doubtful. In the electrocardiogram the pattern of right ventricular hypertrophy in Lead V_1 was found to be evidence of moderate or severe pulmonary hypertension. The degree of prominence of pulmonary arteries, which was demonstrable radiologically in 19 patients, was a good indication of the severity of pulmonary hypertension, though it may be difficult in some cases to exclude other concomitant cardiac lesions.

From this study the author concludes that the degree of pulmonary hypertension in patients with mitral stenosis can be estimated from the clinical, electrocardiographic, and radiological findings without resort to cardiac catheterization.

E. G. Rees

105. **Metabolic Changes Associated with Mitral Valvuloplasty**

G. M. WILSON, I. S. EDELMAN, L. BROOKS, J. A. MYRDEN, D. E. HARKEN, and F. D. MOORE. *Circulation* [*Circulation (N.Y.)*] **9**, 199–219, Feb., 1954. 12 figs., 27 refs.

The authors have investigated the metabolism of patients with mitral stenosis before and after the performance of mitral valvotomy at the Peter Bent Brigham Hospital (Harvard Medical School), Boston. Full metabolic balances were carried out on 3 patients, and estimations of total body water and exchangeable sodium and potassium content by the isotope dilution method in these and 9 other patients, while changes in serum electrolyte levels were studied in 90 additional cases.

In most of the first 12 patients there was no oedema before the operation, but there was an abnormally high body content both of water and sodium, and the total exchangeable potassium content was slightly reduced. Adrenocortical response to the operation (as measured by the eosinophil count and urinary steroid excretion) and changes in nitrogen balance were similar to those occurring after other operations of comparable severity. The changes in electrolyte and water metabolism after mitral valvotomy were qualitatively similar to those occurring after non-cardiac operations, but were quantitatively greater. There was postoperative retention of sodium and water, and the serum sodium and chloride concentrations tended to fall. This last was partly due to excess water retention and in some cases to actual salt deficiency. Restoration of normal equilibrium, with gain of weight, took place gradually over several months following the operation. There was a fall in the total body water and total exchangeable sodium content (extracellular mass) and an increase in the total exchangeable potassium content (lean tissue mass). By difference there was shown to be a clear increase in body fat.

M. D. Milne

CORONARY DISEASE AND MYOCARDIAL INFARCTION

106. Sickness Absence before the First Clinical Episode of Coronary Heart Disease

J. A. HEADY, J. N. MORRIS, F. J. LLOYD, and P. A. B. RAFFLE. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **11**, 20–24, Jan., 1954. 3 refs.

In an attempt to prove the common belief that coronary heart disease strikes healthy people without warning and that it is related to personality, the over-conscientious or ambitious man being principally affected, the authors carried out an investigation amongst drivers and male conductors of central London buses between the ages of 44 and 64, of whom there were approximately 16,000 in 1949. The records of each patient who had a first clinical attack of coronary heart disease in 1949 were compared with those of matched control subjects who had had no such illness. All patients and control subjects were on the active list of employees of the London Transport Executive, and their records included details of their employment and of all absences due to sickness or accident. There were 23 men with coronary heart disease and 77 control subjects.

The investigation showed no significant differences (at the 5% level) in the number of absences per man, the number of days absent per man, or the distribution of absences in a mean experience of 22 years. The men with coronary heart disease had an average of 12·3 absences and 248 days' absence compared with 10·1 absences and 195 days' absence in the control group.

These findings support the idea that coronary heart disease strikes suddenly and without warning, but not that it selects particularly healthy men, the previous sickness absence at the time of the first attack being similar to that of any comparable group of men still in active work.

K. M. A. Perry

107. Heparin Treatment of Patients with Angina Pectoris. Failure to Influence Either the Clinical Course or the Serum Lipids

H. L. CHANDLER and G. V. MANN. *New England Journal of Medicine* [*New Engl. J. Med.*] **249**, 1045–1051, Dec. 24, 1953. 2 figs., 19 refs.

The use of heparin in the treatment of angina pectoris is based on the report by Graham *et al.* (*Circulation* (*N.Y.*), 1951, **4**, 666; *Abstracts of World Medicine*, 1952, **11**, 223) that the parenteral administration of heparin inhibited the development of atherosclerotic lesions in cholesterol-fed rabbits. Contradictory reports have since appeared concerning the effect of heparin on angina pectoris.

At the Boston City Hospital 13 patients aged 34 to 81 with angina pectoris were given intravenous injections of heparin and the effect compared with that of similar injections of a placebo. After a preliminary period of investigation, each patient was given a course of twice-weekly injections of 10 ml. of 5% glucose in water, which he was told would possibly be effective in reducing the frequency of the attacks. After a varying period, and without the knowledge of the patient or the physician, the glucose was replaced by 100 mg. of heparin, the placebo being again administered for a further period later on. The whole experiment lasted for several months, during which the subjects attended as out-patients.

The degree of response was judged from the patient's daily reports (entered on a standard card), his weekly consumption of nitroglycerin tablets (each of 0·4 mg.), changes in response to the Master two-step test, and the physician's own assessment. The authors admit that each of these criteria is open to criticism, and also point out that frequent visits to an interested physician and parental therapy may have beneficial effects in themselves.

Eleven of the 13 patients experienced moderate to marked relief, both subjectively and objectively, from administration of the placebo, and there was no noticeable difference when heparin was substituted or when it was subsequently withdrawn. About 100 days of treatment was needed for maximum improvement. There was no persistent effect on the serum cholesterol level or on the levels of the S_f 12–20 or S_f 20–100 classes of lipoprotein. No haemorrhagic or other untoward effects were noted.

H. David Friedberg

108. Anticoagulants in the Treatment of Cardiac Infarction

A. J. KERWIN. *American Heart Journal* [*Amer. Heart J.*] **46**, 865–882, Dec., 1953. 33 refs.

Either dicoumarol or phenylindanedione was used in the treatment of 301 cases of acute cardiac infarction at the Toronto Western Hospital (University of Toronto); there were 160 control subjects who received no anticoagulant. Patients dying within 72 hours of admission were excluded from the analysis.

The mortality was 17·9% in the treated group and 29·4% in the control group. On further analysis the difference in mortality between the two series was shown to be greater in patients over 60 years of age and to become

evident only after the first week. The mortality among patients who did not have heart failure was the same in both groups, whereas among those with failure the death rate was 33·3% in treated cases and 60·6% in the controls. Thrombo-embolic complications occurred in 7·6% of those receiving anticoagulants and in 20% of the controls. Here again, the difference between the two groups was seen especially in older patients (over 50) and after the second week. Haemorrhagic complications occurred in 18·6% of the treated cases, mostly in those receiving dicoumarol, but there were no deaths from this cause.

Paul Wood

109. **Clinical Aspects of Atypical Myocardial Infarction.** (Die Klinik des atypischen Myokardinfarktes)

G. SCHIMERT. *Zeitschrift für klinische Medizin* [*Z. klin. Med.*] **152**, 2–35, 1953. Bibliography.

In this paper from the University Medical Clinic, Munich, the author expresses the view that atypical cases constitute 30% of all cases of myocardial infarction. He classifies them into four groups, as follows.

(1) Symptomless infarcts, which are found by chance on routine electrocardiography or at post-mortem examination. This group is small, and is often made smaller if the patient is interrogated again in the light of the unexpected finding, when some symptom, until then forgotten, may be recalled.

(2) Painless infarcts, found in patients presenting with symptoms other than pain. Of the two main subdivisions of this group, in the first there may be either signs and symptoms due to a decrease in blood pressure, pulse pressure, and venous pressure, with collapse and shock, or symptoms of autonomic overactivity, with diarrhoea and vomiting, a sense of tiredness and weakness, and perhaps cardiac arrhythmia. Signs of infarction will be found on investigation of the erythrocyte sedimentation rate, leucocyte count, and temperature. In the second subdivision of this group (containing mainly older patients) the symptoms are those of cardiac damage (but without pain), namely, acute or chronic heart failure often accompanied by disturbance of rhythm.

(3) Infarction with atypical pain. In this group the pain may be in the left shoulder or arm, neck, lower jaw, or over the left eye, or may even occur in the right arm; in some cases there is no real pain, but paraesthesiae in the sites mentioned. Patients with upper abdominal pain run the risk of being treated for perforated peptic ulcer. The pain of myocardial infarction may be short-lived, and is not relieved by nitroglycerin—an important distinction from the pain of angina of effort. The author issues a warning against the assumption that no infarct can have occurred if the electrocardiogram is normal, especially if this is taken too soon after the incident.

(4) The masked infarct. Patients in this last group present with signs and symptoms suggesting some condition other than myocardial infarction. Peripheral gangrene may be the first sign of a disturbance of the circulation, or a hemiplegia may result from the lowered cerebral circulation. In other cases the signs and symptoms may be suggestive of pulmonary embolism or pneumonia, while infarction following major surgery is liable to be overlooked altogether.

Throughout his paper the author compares his findings with those of other workers, and there is a useful bibliography.

G. S. Crockett

110. **Hyperglycaemia in Myocardial Infarction.** (L'hyperglycémie de l'infarctus du myocarde)

R. BOULIN, P. UHRY, and H. KAUFMANN. *Presse médicale* [*Presse méd.*] **62**, 77–78, Jan. 23, 1954. 1 fig., 28 refs.

The occurrence of transient hyperglycaemia after myocardial infarction was confirmed in 5 cases examined by the authors within the first 2 days. The maximum blood sugar level ranged from 129 to 206 mg. per 100 ml. and hyperglycaemia or instability of the level persisted for several days. Recognition of this feature is important in order to avoid an erroneous diagnosis of diabetes in such cases. The tentative hypothesis is put forward that this disturbance in carbohydrate metabolism is due to an increased discharge of corticotrophin (ACTH) from the pituitary gland, resulting in increased mobilization of adrenaline and glycocorticoids. This theory is based on the finding, in 2 of the 5 cases, of a concurrent increase in excretion of 11-ketosteroids and 11-oxysteroids associated with a fall in the blood cholesterol level and in the eosinophil count. Acute pancreatic failure, with a fall in insulin production, and hepatic failure with central lobular necrosis—conditions which may be found in states of shock of any aetiology—may contribute to the disturbance.

A. Schott

111. **Norepinephrine in Shock following Myocardial Infarction. Influence upon Survival Rate and Renal Function**

J. J. SAMPSON and A. ZIPSER. *Circulation* [*Circulation (N.Y.)*] **9**, 38–47, Jan., 1954. 4 figs., 22 refs.

The profound hypotension which follows cardiac infarction interferes with the coronary circulation and is mainly responsible for the fatality rate of over 80%. The authors, at the Mount Zion Hospital, San Francisco, have tried the effect of continuous administration of noradrenaline in combating this type of shock, the treatment being given to patients whose systolic blood pressure had been below 100 mm. Hg for one hour or 80 mm. Hg for 15 minutes, or when more than three attacks of hypotension had occurred in 12 hours, or lastly when other pressor substances, such as phenylephrine hydrochloride, had failed. The drug was given in a continuous intravenous drip containing 4 mg. of noradrenaline bitartrate (monohydrate) in 1,000 ml. of 5% glucose solution, saline solutions being avoided because of the known tendency to renal retention of sodium in this type of case. The initial rate of flow was 10 drops per minute intravenously, this rate being later adjusted so as to maintain the systolic blood pressure at about 100 mm. Hg, a level which was usually enough to abolish shock. If more than 40 drops per minute were required, a more concentrated solution was employed. Of the 30 patients thus treated, 19 were male

and 11 female, their ages ranging from 43 to 84 years. In all cases the diagnosis was confirmed electrocardiographically. Three of the patients had previously benefited from blood transfusion and in 16 cases phenylephrine had produced transient improvement.

The treatment was successful in overcoming the immediate shock in 20 cases (67%), although 4 of these patients later died, one from cardiac rupture 8 hours later, one from ventricular fibrillation 19 days later, and 2 others suddenly 4 and 18 days later respectively. Ten patients died during treatment, in most cases shortly after its institution. It is pointed out that in these fatal cases the duration of shock had been twice as long as in the survivors, who also required much smaller doses of the drug.

Oliguria was usual during the period of shock, but improved strikingly after administration of noradrenaline. In 3 patients renal plasma flow increased after cessation of therapy, whereas glomerular filtration rate remained unchanged. Azotaemia was not seen. In one patient noradrenaline appeared to have caused ventricular tachycardia, but generally congestive failure was not aggravated and no other cardiovascular complications were observed.

The authors point out that immediate shock is not as dangerous as delayed shock. They could not confirm the value of distinguishing two types of shock correlated with low and high venous pressures, and are critical of the concept of "irreversible" shock. Nevertheless, they suggest that noradrenaline is most successful when given early. Five illustrative case reports are presented.

F. Starer

BLOOD VESSELS

112. The Elasticity of the Aorta and its Change with Age. (Über die Aortenelastizität und deren Altersveränderungen)

R. WAGNER and E. KAPAL. *Naturwissenschaften* [*Naturwissenschaften*] **41**, 29–33, 1954. 4 figs., 3 refs.

In a study of the effect of age on the elasticity of the aorta, carried out at the University Institute of Physiology, Munich, the authors constructed pressure–volume graphs for the whole thoracic aorta, the data being obtained by means of a tonometer devised by the senior author and an optical registering apparatus. The materials used in the study were post-mortem specimens of the human and bovine aorta.

The volume of the aorta plotted on the abscissa against pressures up to 250 mm. Hg on the ordinate resulted in an S-shaped curve, which for young human and bovine specimens showed a steep rise of pressure at the beginning of filling, followed in the next part by an almost linear increase of volume with corresponding increase in pressure—that is, in the region of normal physiological blood pressure—while the last part of the curve showed a steep rise of pressure for a small rise of volume. This characteristic curve shows that the aorta acts as a pump-reservoir or expansion chamber, transforming the intermittent cardiac output into a continuous flow.

It is then proved mathematically that the angle formed between a tangent to the curve at any point and the abscissa is a function of the distensibility of the aorta, thus confirming that dilatation of the aorta in the normal physiological range of blood pressure causes least work to the heart, that is, within this range the aorta acts best as a reservoir for the cardiac output. The linear relation between pressure in the aorta and its volume is therefore important for the regulation of blood pressure, which is mediated through stretch receptors in the aortic wall. The authors demonstrate that the volume–pressure curve of a piece of rubber tubing is quite different from that of the aorta, the main difference being due to the structure and material of the aorta. On repeated stretching and relaxation of the aorta it was found that the relaxation curve ran parallel to, but below, the distension curve; this period of hysteresis became smaller on repeated stretching and was always minimal in the region of physiological blood pressure.

With increasing age the first, steep, part of the curve was shown to become flatter and therefore to make a smaller angle with the abscissa; this increased distensibility in the lower range of the volume–pressure relation is due in part to replacement of elastic tissue by collagenous connective tissue which has a different mechanical behaviour, and also in part to a change in the tissue itself which may be compared to the "fatigue" which develops in metals.

Ferdinand Hillman

113. The Effects of Peripheral Arterial Embolism

R. L. RICHARDS. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **23**, 73–90, Jan., 1954. 2 figs., 35 refs.

This review from the University of Glasgow of the effect of embolism of the peripheral arteries is based on a survey of the literature and on personal observation in 52 cases (56 episodes of peripheral arterial embolism). Of the 52 patients, 15 recovered completely and 20 died; the remaining 17 had post-embolic ischaemia. Treatment included embolectomy in 19 cases and amputation of a limb in 4; the remaining cases were treated conservatively. The author states that he has seen only 4 cases "in which, without embolectomy, recovery of function in the limb was complete within 72 hours of the occurrence of the first symptom", the upper limb being affected in all 4 cases.

Discussing the sequence of events when an embolus becomes lodged in a peripheral artery, the author points out that in the majority of cases the embolus is derived from a cardiac thrombus. Although soft in texture, the embolus is subjected to the hammering effect produced by the onward thrust of the blood at each cardiac systole. Because of a fall in blood pressure, there is constriction in the distal portion of the main vessel and its branches. Constriction sometimes occurs proximally, but this phenomenon is probably due to a nervous reflex. The effects are less pronounced when a second embolism causes obstruction at a proximal site.

As regards the clinical features, a sudden transient pain may be felt in the limb at the site of the embolism. This pain arises from stimulation of the nerve endings in the arterial wall, the stimulus being associated with

distension rather than spasm. The principal pain is due to ischaemia of the tissues; it develops gradually and is maximal on the distal side of the occlusion. Either numbness or coldness of the limb precedes pain in approximately one-third of all cases. The degree of paralysis varies considerably. At first the muscles are of normal consistency, but contractures develop after a period of approximately 6 hours, when the muscles are found to be firm on palpation. Subsequently muscular softening takes place and the tenderness diminishes. The late effects of paralysis are often troublesome and are occasionally followed by permanent disability.

It is concluded that medical treatment should be instituted if the patient is seen within 8 hours of the onset of symptoms. Embolectomy is advised, however, if no improvement is observed after 2 to 3 hours.

A. Garland

114. **Phlegmasia Caerulea Dolens**

P. MARTIN. *British Medical Journal* [*Brit. med. J.*] **2**, 1351–1353, Dec. 19, 1953. 18 refs.

The name phlegmasia caerulea dolens was first suggested by DeBakey and Ochsner (*Surgery*, 1949, **26**, 16; *Abstracts of World Surgery*, 1950, **7**, 64) to describe the condition of the lower limb which occurs when almost the whole of the venous outflow of the leg is blocked, usually by thrombosis. The condition is a much more severe variant of the more common deep femoral thrombosis (or white leg), and has also been termed by various authors pseudo-embolic phlebitis, blue phlebitis, and gangrenous thrombophlebitis. The onset of the condition is characterized by severe pain and swelling in the affected limb, shock, a cyanotic tint, and complete absence of the distal pulses. The condition (apart from the swelling) may be difficult to differentiate from arterial embolism. Usually the condition responds quite rapidly to conservative treatment such as elevation of the foot of the bed and the administration of heparin and tolazoline by mouth, but occasionally peripheral gangrene may develop.

After citing a few illustrative cases from the literature, the author discusses the part played by arterial spasm in the production of the clinical picture, but implies that the evidence in favour of this is not very impressive. Treatment as indicated above, with induction of deep sleep by amylobarbitone or morphine, is advocated. The affected limb should be kept at room temperature and, when the patient is fit enough, actively exercised under the supervision of a physiotherapist. Sympathectomy is not considered to be helpful. If amputation for gangrene becomes necessary, this should be limited to the removal of the dead tissue only, as the circulation to the rest of the limb has always completely recovered before the need for amputation arises.

F. B. Cockett

115. **Parenteral Trypsin in Peripheral Vascular and Thromboembolic Diseases**

M. M. FISHER and N. D. WILENSKY. *New York State Journal of Medicine* [*N.Y. St. J. Med.*] **54**, 659–662, March 1, 1954. 12 refs.

SYSTEMIC CIRCULATORY DISORDERS

116. **Malignant Growths (Including Leukaemia) and Essential Hypertension**

S. G. ZONDEK and M. TCHETCHIK. *British Journal of Cancer* [*Brit. J. Cancer*] **7**, 418–422, Dec., 1953. 3 refs.

It has previously been demonstrated that the incidence of carcinoma is reduced in persons suffering from essential hypertension (Zondek, *Brit. J. Cancer*, 1952, **6**, 131; *Abstracts of World Medicine*, 1953, **13**, 298). The present paper, from the Hadassah Municipal Hospital, Tel-Aviv, Israel, records a similar study of the relationship between essential hypertension and sarcoma and leukaemia.

Among 133 men aged 40 to 69 suffering from sarcoma or leukaemia, the incidence of hypertension was 3% compared with the usual figure of 18 to 20% for the whole population in this age group. Among 62 women aged 40 to 59 suffering from these diseases, 8·0% had hypertension compared with the usual incidence of 18 to 24%. Only those cases were included in which the general condition was still satisfactory and in which the blood pressure before the onset of the malignant disease was known.

M. Lubran

117. **Comparison of Various Vascular Beds in Man. Their Responses to a Simple Vasodilator Stimulus**

W. REDISCH, L. WERTHEIMER, C. DELISLE, and J. M. STEELE. *Circulation* [*Circulation (N.Y.)*] **9**, 63–67, Jan., 1954. 4 figs., 27 refs.

In view of the paucity of knowledge regarding the interplay between the various vascular beds in man in health and disease, the authors, in an investigation carried out at New York University College of Medicine, studied the renal blood flow and that in the extremities in 11 normal subjects, 6 hypertensive patients, and 10 patients with peripheral vascular disease affecting the lower limbs. Measurements were made at rest and following a vasodilator stimulus (immersion of a limb in water at 45° C.) in an environment kept at 20° C. and 50 to 55% humidity. Renal blood flow was calculated from renal plasma flow, which was estimated from the haematocrit value and determination of clearance of PAH by a constant infusion technique. Extremity blood flow was measured by a specially designed air-transmission plethysmograph employing a strain gauge to measure volume changes in terms of pressure changes as small as 3 or 4 mm. Hg, too small to affect blood flow (this apparatus is described in detail). Plethysmographic readings were obtained for the foot, leg and foot, hand, and arm and hand. From anatomical considerations it was considered that the plethysmographic recordings from the hand or foot represent predominantly blood flow through the skin, whereas those of forearm or leg represent predominantly blood flow through deeper tissues, mainly muscle.

Results showed that the vasodilator stimulus produced reflex vasodilatation in the non-immersed extremities and simultaneous decrease in renal blood flow (maximum decrease 10 to 13%) in all 3 groups of subjects.

In the normal and hypertensive subjects the basal blood flow in the extremities was comparable, and also responses to reflex vasodilatation were similar. The patients with peripheral vascular disease had lower basal blood flow in the foot, but a higher basal blood flow in the hand, possibly as a compensatory mechanism for the elimination of body heat; these patients also had delayed and diminished response to the vasodilator stimulus. The inverse relationship between renal blood flow and extremity blood flow is of interest, though not unexpected in view of the known fact that the renal blood flow falls in a hot environment or after heating the body by diathermy. *K. G. Lowe*

118. **Comparison of Visceral and Peripheral Vascular Beds in Hypertensive Patients. Their Responses to Various " Hypotensive " Drugs**
W. REDISCH, L. WERTHEIMER, C. DELISLE, and J. M. STEELE. *Circulation* [*Circulation* (*N.Y.*)] **9**, 68–72, Jan., 1954. 2 figs., 27 refs.

Using the techniques described in their previous paper [see Abstract 117] the authors have studied the changes in extremity and renal blood flows following the intravenous administration of hypotensive agents to 8 patients with moderate or severe essential hypertension.

Hexamethonium, " ilidar " (a dibenzazepine phosphate), and " hydergine " (an equal mixture of three dehydrogenated alkaloids of ergot) increased the extremity blood flow and reduced the renal blood flow. Protoveratrine (an alkaloid of veratrum album) reduced renal blood flow without significantly affecting extremity blood flow. " Apresoline " (hydrallazine) increased renal blood flow and lowered extremity blood flow, causing a fall in digital temperature. In 2 paraplegic patients with normal blood pressure, hydrallazine increased extremity blood flow, but renal blood flow remained unaffected. This effect of hydrallazine was also obtained on the sympathectomized side of a hypertensive patient who had undergone unilateral subtotal sympathectomy, although the expected response (that is, increased renal blood flow and lowered extremity blood flow) was elicited on the opposite side. " Regitine " did not appreciably affect either renal or extremity blood flow. *K. G. Lowe*

119. **Investigation by Cardiac Catheterization of the Circulatory Changes during Severe Hypotension Induced by Hexamethonium.** (Herzkatheter-Untersuchungen bei massiver Blutdrucksenkung durch Hexamethonium)
H. VETTER, G. GRABNER, F. MLCZOCH, and K. STEINBEREITHNER. *Klinische Wochenschrift* [*Klin. Wschr.*] **32**, 97–103, Feb. 1, 1954. 8 figs., 5 refs.

At the University Medical Clinic, Vienna, 16 subjects were given hexamethonium and the effect on the cardiovascular system observed by means of cardiac catheterization, the blood pressure being also continuously recorded and blood gas levels estimated. The subjects were aged between 18 and 63 years; in 3 of them the cardiovascular system was normal, 5 suffered from hypertension, and the remaining 8 had various diseases of the heart and lungs. The dose of hexamethonium (50 to 200 mg. in doses of 50 mg. intravenously) was sufficient to reduce the blood pressure of the recumbent patient to 60 mm. Hg.

With the fall in systemic blood pressure a fall in pulmonary arterial and venous filling pressures also occurred. The oxygen consumption of some patients increased and of some decreased, but the average for the whole group remained unchanged. The arterial oxygen saturation was little changed, but a lowering of the venous oxygen saturation increased the arterio-venous oxygen difference. During the period of lowered blood pressure the cardiac output was reduced, and the peripheral resistance in both systemic and pulmonary circulations fell. The effective work of both ventricles was decreased.

The theoretical and practical meaning of these circulatory changes is discussed in the light of the application of hexamethonium therapy to conditions of hypertension in the pulmonary and systemic circulations. *H. E. Holling*

120. **Clinical Evaluation of Combined Hydrogenated Ergot Alkaloids (Hydergine) in Arterial Hypertension. with Special Reference to Their Action in Central Manifestations**
R. M. TANDOWSKY. *Circulation* [*Circulation* (*N.Y.*)] **9**, 48–56, Jan., 1954. 15 refs.

At Los Angeles County Hospital, " hydergine " (an equal mixture of 3 hydrogenated ergot alkaloids) was given intravenously in a dose of 0·3 mg., diluted with saline, at 15-minute intervals for 2 hours to 78 patients with sustained hypertension; this group comprised 33 female patients (average age 51 years) and 45 males (average age 56 years). Another group of 22 patients (11 female and 11 male, average age 55·8 years) were given hydergine as emergency treatment for hypertensive encephalopathic symptoms, chiefly intractable headache, aphasia or hemiplegia of short duration, fits, confusion, giddiness, nausea, tinnitus, and syncope.

The average reduction in blood pressure for the first group of 78 patients was 36 mm. Hg systolic and 12 mm. Hg diastolic during the 2-hour period following administration of hydergine, and the average reduction in pulse rate was 6 beats per minute. In some of the younger patients the fall in blood pressure was drastic, and one patient had severe hypotension while another showed apprehension and hyperventilation, but both recovered; 24 patients complained of " nasal stuffiness " and 6 had paraesthesiae. The 22 encephalopathic patients showed an average maximum fall in blood pressure of 40·5 mm. Hg systolic and 20·7 mm. Hg diastolic, and an average reduction in pulse rate of 9 beats per minute. In the majority of cases there was marked improvement in all symptoms except insomnia, for which sedation was required. Early mild hemiplegia was completely relieved in 6 out of 7 cases in which it was present. The author concludes that although the short-lived hypotensive action of hydergine renders it of little practical value in the ambulant treatment of hypertensive patients, the drug probably has a useful place in the emergency treatment of hypertensive encephalopathy. *K. G. Lowe*

121. **The Effect of Single Intravenous and Oral Doses of McN-181 (1:4-Bis(1:4-benzodioxan-2-ylmethyl) Piperazine) upon the Blood Pressure of Hypertensive Subjects**
W. H. ROSENBLATT, T. A. HAYMOND, S. BELLET, and G. B. KOELLE. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 179–185, Feb., 1954. 13 refs.

McN-181 or "dibozane", an adrenergic blocking agent, was administered by intravenous infusion to 6 hypertensive patients on 14 occasions in doses ranging from 23 to 94 mg., and orally to 5 patients on 6 occasions in doses of 0·75 to 1·05 g.

Moderate reduction in systolic and diastolic pressure (30/20 or greater) occurred during or following intravenous infusion on 6 occasions; slight falls (20/10 to 30/20) occurred twice, no significant changes in pressure (<20/10) 4 times, and a predominantly pressor effect was noted twice in one patient. The hypotensive effect usually persisted 30 to 60 minutes after infusion. Relatively slow infusion of a given dose generally resulted in a greater fall in blood pressure and less increase in heart rate than did more rapid infusion of the same dose in the same patient. The possible basis of the difference is discussed. Side effects noted most frequently were drowsiness, slight to marked increase in heart rate, and dizziness. Varying degrees of reduction in blood pressure occurred in 5 of the 6 oral trials, and persisted from one to over 5 hours. The fall was profound in one patient.

It is concluded that McN-181 is capable of reducing blood pressure in certain patients with essential hypertension, but that there is considerable individual variation with respect to its absorption and effectiveness. In view of its potency, low toxicity, and apparent lack of gastrointestinal irritation, the drug appears worthy of consideration for long-term assessment for the treatment of hypertension.—[Authors' summary.]

122. **The Use of Apresoline in the Hypertensive Arteriosclerotic Syndrome**
J. KLEH and J. F. FAZEKAS. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 57–64, Jan., 1954. 9 refs.

The effect of "apresoline" (hydrallazine) on hypertension and arteriosclerosis in the aged patient was studied at the District of Columbia General Hospital and Home for Aged and Infirm, Washington, D.C. The subjects were 10 women and 7 men aged 51 to 81 with persistent diastolic hypertension, and 2 men and 1 woman aged 79 to 91 years with normal blood pressure but symptoms of cerebral arteriosclerosis. Daily clinical reports and twice-daily blood-pressure readings were made by nurses, and cerebral blood flow, cerebral vascular resistance, and cerebral basal metabolic rate were estimated in each case. After a control period, apresoline was given in doses of 25 mg. 4 times daily, increasing by 25 mg. a dose every 2 to 5 days. A placebo was substituted for a varying period during the test in about half the cases.

In 14 of the cases of hypertension there was significant improvement, with an average reduction in systolic blood blood pressure of 45 mm. Hg and in diastolic pressure of 26 mm. Hg. A smaller reduction in pressure was achieved in the cases of normotensive cerebral arteriosclerosis. In most of the 7 hypertensive patients who received the placebo the blood pressure returned gradually to the original level, and in 4 cases hypertensive encephalopathy developed and apresoline treatment had to be reinstituted. A mean increase in cerebral blood flow of 23% and a mean reduction in cerebrovascular resistance of 26·5% occurred during treatment. Thus even in cases of cerebral arteriosclerosis the vessels are capable of compensating for a reduction in pressure by increasing their diameter.

However, in spite of the increased delivery of oxygen to the brain there was no increased utilization of it, though there was objective and subjective improvement in clinical manifestations normally attributed to cerebral anoxia. Nor was any correlation found between the rate of cerebral blood flow and the clinical condition in individual cases, either before or during apresoline therapy, so that the improved mental status noted may not be directly related to haemodynamic changes. *Peter Harvey*

123. **1-Hydrazinophthalazine (Apresoline) in Hypertension**
E. HARRIS and R. TURNER. *Lancet* [*Lancet*] **1**, 429–433, Feb. 27, 1954. 34 refs.

The main pharmacological actions of "apresoline" (hydrallazine) as reported in the literature by various authors are summarized under 11 headings. It is suggested that the drug reduces vasoconstrictor tone, thus lowering the blood pressure, and that the resulting increase in cardiac output may be secondary. The authors then report the results of a clinical trial of the drug on 22 hypertensive patients at the Western General Hospital, Edinburgh, in all but 3 of whom the hypertension was severe (Smithwick's Groups III or IV). An initial dose of 25 or 50 mg. of hydrallazine 8-hourly was increased every few days by 25 mg. (75 mg. per day) until frequent readings of the blood pressure after a given dose showed an adequate response, which is defined as a 20% reduction in diastolic pressure for at least 3 hours. When adequate reduction of blood pressure was attained the patients were discharged from hospital and thereafter attended as out-patients, at first weekly and later at 4- or 6-weekly intervals.

Initially, 8-hourly doses produced a 24-hour reduction of the blood pressure with daily doses up to 1,200 mg. After a period of about 10 days' treatment, however, the dose needed to produce an adequate response had to be steadily increased, and eventually treatment usually had to be stopped in less than one month because of tolerance to the drug, or because of toxic symptoms. Side-effects were common and consisted in headache, palpitation, retrosternal discomfort, weakness, nausea and vomiting, and cutaneous complications. The complication which most often tended to subside in spite of continuing treatment was the headache. The authors conclude that hydrallazine given as the sole hypotensive drug is of little value in treating hypertension of severe degree, and suggest that their results are at variance with those of some other workers because their own cases were more

severe and the period of observation longer. However, as hydrallazine has some useful properties, notably its action on renal blood flow, they find it difficult to reject the drug altogether, and suggest that a combination of hydrallazine with a ganglion-blocking agent might be more successful. *D. W. Barritt*

124. **Clinical Appraisal of Intra-arterial Priscoline Therapy in the Management of Peripheral Arterial Diseases**

A. G. PRANDONI and M. MOSER. *Circulation* [*Circulation (N.Y.)*] **9**, 73–81, Jan., 1954. 21 refs.

The intra-arterial use of vasodilators might be expected to avoid some of the undesirable systemic effects of intravenous autonomic blocking agents. The injection into the femoral, radial, or brachial artery of " priscoline " (benzazoline; 2-benzyl-4 : 5 imidazoline hydrochloride), which has an adrenergic blocking and direct vasodilator action and is neither necrotizing to tissue nor irritant to the vascular endothelium, was therefore tried by the authors in the treatment of 250 patients with peripheral vascular disease at the Walter Reed Army and George Washington Unjversity Hospitals, Washington, D.C. They point out the importance of giving the injection slowly, and state that 50 to 75 mg. produces a maximal effect. In normal subjects a rise in skin temperature occurred in 15 to 90 seconds, and was accompanied by a marked increase in arterial pulsation.

The results were fairly satisfactory. Of 7 cases of Raynaud's disease improvement with healing of ulcers in 5 resulted, even when previous sympathectomy had been unsuccessful. There has been no serious relapse in these cases after 6 to 18 months' observation. In a miscellaneous group of 38 patients with " causalgic type " pain the results were uncertain and difficult to evaluate, but some were very satisfactory. In the treatment of 65 patients with arteriosclerosis obliterans the best results were obtained in those with ischaemic rest pain, but increased exercise tolerance was obtained in only a few. Skin temperature was raised in all but 21 cases, while in 9 cases a fall was observed. Of a group consisting of 50 men and one woman with thromboangiitis obliterans, all had previously received various forms of treatment, including benzazoline by mouth, without success. Gangrene was present in 26 cases. Of the 51 patients, 14 obtained complete and 10 partial relief, improvement being greater in those who had given up smoking. Only 3 in the whole group required subsequent amputation. Exercise tolerance, however, was but rarely increased.

In the management of 12 patients with sudden arterial embolism or thrombosis, the development of gangrene could not be entirely prevented in 7 cases, but only limited amputation was required in 3 cases; in the others the gangrenous areas healed, and anticoagulant therapy could be combined with the injections of benzazoline. In 9 of these patients, however, the drug caused paradoxical reduction in blood flow to the foot.

The authors conclude that intra-arterial administration of benzazoline does not increase blood flow as much as autonomic blocking agents, such as hexamethonium. They found, moreover, that changes in blood flow, as judged by skin temperature and plethysmography, did not always correlate with the clinical results. They believe that benzazoline produces its best results given by the intra-arterial route. No serious complications were observed in some 2,000 injections, but tolerance to the drug may develop. They finally conclude that although hexamethonium and " dibenzyline " frequently give better results, benzazoline by intra-arterial injection has a place where a possible reduction in blood pressure is undesirable, but that " uniformly good results should not be expected ". *F. Starer*

PULMONARY CIRCULATION

125. **Complete Anomalous Pulmonary Venous Drainage**

J. D. KEITH, R. D. ROWE, P. VLAD, and J. H. O'HANLEY. *American Journal of Medicine* [*Amer. J. Med.*] **16**, 23–38, Jan., 1954. 10 figs., 23 refs.

The authors describe 14 cases of total anomalous pulmonary venous drainage into the right side of the heart which were examined at the Hospital for Sick Children, Toronto, the diagnosis being confirmed post mortem in 13, and add these to 45 proved cases culled from the literature. The pulmonary veins drained into a left-sided superior vena cava in 43% of the 58 proved cases, into the coronary sinus in 19%, into the right atrium in 14%, into a right-sided superior vena cava in 12%, and in the remainder into the portal vein, ductus venosus, or superior vena cava and right atrium. Of the 58 patients, 47 (80%) died in the first year of life, and all the remainder before the age of 8 years, with the exception of one who survived to the age of 27.

Cyanosis was not significant in the cases studied by the authors, the arterial oxygen saturation ranging uniformly between 80 and 95%, with one exception in which it was 63%. A continuous murmur in the pulmonary area, which did not wax and wane like the murmur of patent ductus arteriosus, was heard in 4 of the proved cases and was regarded as a venous hum. Radiographs in the cases in which the pulmonary veins drained into the left superior vena cava showed the typical anomalous bilateral venous arc superimposed on the base of the heart when the patient was over 6 months old, but was by no means obvious in those dying in the first few weeks of life; nor was it seen when the pulmonary veins drained into the coronary sinus, right superior vena cava, or right atrium. An interesting feature of the electrocardiogram was the presence of a Q wave in right precordial leads in all but one of the cases.

Cardiac catheterization was carried out in 4 of the authors' cases and in 9 others, the characteristic finding being of highly arterialized blood in all chambers of the heart, with no material difference in oxygen saturation in any of the samples. When the pulmonary veins drain direct into the right atrium, however, the findings are less specific. Evidence of an atrial septal defect or patent foramen ovale was found in only one of the authors' 4 cases. Surgical correction of the defect was not attempted. *Paul Wood*

Haematology

126. **Experimental Agranulocytosis. Its Production through Leukocyte Agglutination by Antileukocytic Serum.** [In English]
S. MOESCHLIN, H. MEYER, L. G. ISRAELS, and E. TARR-GLOOR. *Acta haematologica* [*Acta haemat. (Basel)*] **11**, 73–94, Feb., 1954. 12 figs., 38 refs.

At the Zürich University Medical School an antiserum to guinea-pig granulocytes was prepared by injecting rabbits with a suspension of cells obtained from the peritoneal cavity of a guinea-pig, the rabbit serum being inactivated at 57° C. and haemolysins removed by absorption with guinea-pig erythrocytes.

The intracardiac injection of this antiserum into guinea-pigs was followed within an hour by a profound granulocytopenia with subsequent recovery; the cells which disappeared from the peripheral blood were shown to have been agglutinated and filtered off in the lungs. Subcutaneous injection of the antiserum caused a more prolonged granulocytopenia; the bone marrow at first showed the disappearance of mature cells, then an increase in myelocytes and promyelocytes, which became larger than usual. Corticotrophin (ACTH) had no effect on the blood or marrow changes, but prolonged survival.

It is concluded that if the peripheral destruction of granulocytes owing to some immunological mechanism, such as drug sensitization, primary atypical pneumonia, or Felty's syndrome, occurs only for a short time, the marrow picture will be almost normal, whereas more prolonged destruction will cause a hyperplasia of marrow with a predominance of immature forms (maturation arrest). Ultimately the only surviving cells might be non-granular cells, although this was not demonstrated experimentally. *George Discombe*

127. **Use of Purified Prothrombin in the Study of Hemophilia and Plasma Thromboplastin Component (PTC) Deficiency**
S. A. JOHNSON and W. H. SEEGERS. *Journal of Applied Physiology* [*J. appl. Physiol.*] **6**, 429–436, Jan., 1954. 4 figs., 36 refs.

Working at Wayne University College of Medicine, Detroit, the authors have devised an assay procedure for studying the activity of those factors in plasma and serum which function together with platelet ac-globulin and calcium in the activation of prothrombin. Purified prothrombin, platelet ac-globulin, and calcium chloride are mixed with the plasma or serum under test, and the rate of thrombin formation in this mixture is measured quantitatively. With normal blood, thrombin formation is slower when serum is used than with plasma, this difference in rate being referred to as the plasma–serum (P–S) difference. Haemophilic serum and plasma show no such difference, their thromboplastic activity being equivalent to that of normal serum. In cases of deficiency of plasma thromboplastin component there is a P–S difference, but both plasma and serum are less active than normal plasma or serum. In refractory haemophilia, that is, haemophilia which no longer shows any improvement after the transfusion of normal plasma, the activity of serum and plasma is the same and is similar in degree to that found in ordinary haemophilia, but the amount of normal plasma which must be added to the haemophilic plasma to produce normal results is much greater than in cases of non-refractory haemophilia. The thromboplastic activity of normal serum and of serum and plasma from these abnormal bloods can be increased to that of normal human plasma by repeated extraction with ether. It is suggested that in these haemorrhagic diseases the material which causes the normal P–S difference is already covered or conjugated with an inhibitor, and the reduced activity that remains, equivalent to that of normal serum, is not sufficient for normal haemostasis; in refractory haemophilia the inhibitor is present in even greater quantity.

The authors consider that the assay procedure used in this investigation has possibilities in the diagnosis and treatment of bleeding diseases. Thus deficiency of plasma thromboplastin component could be differentiated from classic haemophilia, and it would also be possible to measure the effect of the various substances on prothrombin activation in haemophilia.

R. F. Jennison

128. **Myelomata of Bone. A Review of 25 Cases**
A. NAYLOR and F. E. CHESTER-WILLIAMS. *British Medical Journal* [*Brit. med. J.*] **1**, 120–124, Jan. 16, 1954. 2 figs., 9 refs.

This review of 25 cases of myelomata of bone is presented because, in the authors' view, these tumours are not so rare as is generally believed, 24 of the 25 cases having been seen at Bradford and Keighley Hospitals over a recent 5-year period, as against 13 cases of osteogenic sarcoma during the same period. The authors describe three types of tumour formation: (1) a large single tumour—the solitary form; (2) numerous small lesions causing diffuse decalcification of a bone—the diffuse form; and (3) scattered osteolytic lesions throughout the skeleton—the multiple form, into which the other two forms ultimately develop. It is pointed out that the diagnosis of solitary myeloma (plasmacytoma) is determined by the results of histological examination of biopsy specimens, radiological examination of the whole skeleton, and the Bence Jones test for proteose in the urine, the results of which are negative. The solitary form was found in the younger age group, and was three times as common in males as in females. The diffuse and multiple forms were usually found in older age groups, and females were more often affected than males. Diagnostic procedures included, in addition to *x*-ray examina-

tion, estimation of the serum protein level and albumin: globulin ratio, examination of the sternal marrow, and the Bence Jones test for proteose in the urine. A high erythrocyte sedimentation rate was a frequent finding, but changes in the blood count were a late manifestation of the disease. Presenting symptoms were usually pain, especially backache, and in some cases pathological fracture and paraplegia.

Treatment was disappointing: stilbamidine was of little value, but deep *x*-ray therapy helped to relieve pain and to prevent the onset of paraplegia. One of the authors' patients survived 7 years after deep *x*-ray therapy of a solitary tumour.

The authors stress the need for early diagnosis. They consider that the present-day text-book description of multiple myeloma is that of the end-stage of the disease.

R. D. S. Rhys-Lewis

129. Blood Cell Count Response to Infusion of Polymeric Glucose

S. M. HORVATH and L. H. HAMILTON. *American Journal of Physiology* [*Amer. J. Physiol.*] **176**, 319–321, Feb., 1954. 5 refs.

The effect of infusion of a 6% solution of polymeric glucose (average molecular weight 39,000) on the leucocyte and erythrocyte counts in the peripheral venous blood of dogs which had suffered a controlled haemorrhage was studied at the State University of Iowa. A marked leucocytosis, principally due to an increase in the neutrophil count, was observed and persisted for more than 24 hours. The eosinophil count decreased early in the period following infusion, none of these cells being seen the day after the infusion. The erythrocyte response apparently did not reflect simple changes in blood volume.

G. B. West

ANAEMIA

130. New Observations on Sickle Cells. With Special Reference to Their Agglutinability

M. BESSIS, M. BRICKA, J. BRETON-GORIUS, and J. TABUIS. *Blood* [*Blood*] **9**, 39–45, Jan., 1954. 4 figs., 13 refs.

This article from the National Blood Transfusion Centre, Paris, describes both direct and cinematographic observations of the sickling phenomenon by phase-contrast and electron microscopy. As a preliminary to sickling, the haemoglobin in the interior of the erythrocyte appears to be rearranged so as to form 2 or 3 large, irregular masses while the cell still retains its plasticity and rounded contour. The cell next becomes rigid, changes shape from the development of the characteristic spicules, and loses the oscillatory movement of the normal cell. While the spicules developed by discoidal erythrocytes are all in the same plane, spherocytes on reduction give rise to crenated spheres with rigid spicules pointing in all directions. The myelin forms, both attached and free, also become rigid and probably therefore contain haemoglobin. [For details of the architecture of sickled cells the excellent photomicrographs reproduced in this article should be studied.]

The erythrocytes of sickle-cell anaemia in the presence of oxygen can be agglutinated by antisera in the normal way, but after reduction they do not agglutinate. The authors consider this to be due to their failure to form the viscous threads which they believe to be responsible for normal agglutination.

Nigel Compston

131. The Life Span of the Elliptocyte. Hereditary Elliptocytosis and Its Relationship to Other Familial Hemolytic Diseases

A. G. MOTULSKY, K. SINGER, W. H. CROSBY, and V. SMITH. *Blood* [*Blood*] **9**, 57–72, Jan., 1954. 2 figs., bibliography.

Hereditary elliptocytosis is not usually associated with any evidence of increased erythrocyte destruction, but occasionally there is laboratory evidence of excessive haemolysis, and rarely anaemia may occur. It must be distinguished from conditions in which ovalocytes or elliptocytes occur as a result of anisocytosis and poikilocytosis, true elliptocytosis being indicated by the preponderance of elliptical cells and by its familial occurrence. The present authors describe 3 cases of elliptocytosis, in only one of which was there evidence of increased haemolysis. Erythrocyte survival was studied both by the Ashby differential agglutination technique and by a visual method in which the recipients were patients with sickle-cell anaemia, the detection of surviving elliptocytes being facilitated by first sickling the host cells. Erythrocyte survival time was reduced in the case with excessive haemolysis, but was normal in the other two cases.

The relationship of hereditary elliptocytosis to other forms of hereditary haemolytic anaemia is discussed, and it is postulated that inheritance is of the same pattern as that of thalassaemia, but that homozygous cases are rare because of the infrequency of occurrence of the gene amongst the population. The varying degrees of affection of heterozygotes finds a parallel in thalassaemia minor.

Nigel Compston

132. Direct Observations of Intravascular Agglutination of Red Cells in Acquired Autoimmune Hemolytic Anemia

C. WASASTJERNA, W. DAMESHEK, and Z. D. KOMNINOS. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **43**, 98–106, Jan., 1954. 32 refs.

Divergent opinions have been expressed regarding the mechanism and significance of the intravascular clumping of erythrocytes which occurs in many pathological conditions. At the New England Center Hospital and Tufts College Medical School, the authors studied the appearance of the blood in the superficial vessels of the conjunctival sclerae by slit-lamp microscope in 15 presumably healthy subjects and 53 patients with haematological disorders, the special purpose of the investigation being to determine whether the antibody-coated erythrocytes in cases of acquired haemolytic anaemia underwent agglutination *in vivo*. Although slight to marked auto-agglutination was visible in the blood in all 14 cases of acquired haemolytic anaemia studied, and although the intensity of the agglutination seemed to be correlated

with the severity of the haemolytic process, similar degrees of agglutination were seen in other severely ill patients not suffering from a haemolytic disorder.

The authors conclude that although auto-agglutination may be an important factor in the causation of haemolysis in acquired haemolytic anaemia, the fact that apparently similar degrees of agglutination may be seen in non-haemolytic states suggests that other mechanisms must play a part in the haemolysis of antibody-coated erythrocytes. The relationship between auto-agglutination and the " sludging " of blood—the term used by Knisely—is considered, and the conclusion reached that the latter is probably more closely related to rouleau formation than to true agglutination. *J. V. Dacie*

133. **Haemolytic Anaemia of the Newborn with Spontaneous Formation of Inclusion Bodies. A New Syndrome Observed in 14 Cases.** (Die hämolytische Frühgeburtenanämie mit spontaner Innenkörperbildung. Ein neues Syndrom, beobachtet an 14 Fällen)
C. GASSER. *Helvetica paediatrica acta* [*Helv. paediat. Acta*] **8**, 491–529, Dec., 1953. 13 figs., 26 refs.

The author reports, from the University Paediatric Clinic, Zürich, an unusual form of haemolytic anaemia characterized by spontaneous formation of inclusion bodies, which was observed in 14 newborn babies, including two sets of twins and one surviving twin (the other one being dead at birth). All the infants were premature or underweight and developed jaundice in the first week of life and marked anaemia in the second and third weeks, often severe enough to require blood transfusion. In some of the infants over 90% of the erythrocytes developed inclusion bodies, vital dye preparations being sometimes required for demonstration of these. Reticulocytosis usually followed the crisis, and erythroblasts were occasionally seen in small numbers in the peripheral blood. Spherocytosis was not a feature, and there was no abnormal erythrocyte fragility. Further, no splenomegaly or lymph-node enlargement was observed in any of the cases, no significant antibodies were detected in the mothers or babies, and there was no history of exposure to toxic agents either during pregnancy or at birth.

The aetiology is discussed in relation to splenic dysfunction, disorders of haemoglobin synthesis, and immune-body reactions, but no definite conclusion is reached. It is suggested that the existence of such a blood disorder be borne in mind when considering the case of a newborn child with persisting icterus in whom there are no other significant clinical features and no evidence of blood incompatibility. *Mary D. Smith*

134. **Studies of Vitamin B_{12} in Serum and Urine following Oral and Parenteral Administration**
W. G. UNGLAUB, H. L. ROSENTHAL, and G. A. GOLDSMITH. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **43**, 143–156, Jan., 1954. 6 figs., 30 refs.

The authors determined the level of vitamin B_{12} (cyanocobalamin) in the serum and urine before and after its oral and parenteral administration to 31 normal subjects and to 8 patients with Addisonian pernicious anaemia in relapse or with nutritional macrocytic anaemia at the Charity Hospital of Louisiana (Tulane University), New Orleans. The assays were carried out microbiologically with *Lactobacillus leichmannii*. They report that the resting total serum vitamin-B_{12} activity was lower in patients with macrocytic anaemia than in normal subjects, though the levels in the urine were the same. After the intramuscular injection of 10 to 100 μg. of crystalline vitamin B_{12} the serum and urine levels rose both in the normal subjects and in 2 patients with pernicious anaemia. Oral administration of the vitamin had little effect on the serum level in normal subjects unless doses as high as 3,000 μg. were given, whereas in 2 out of 3 of the patients with macrocytic anaemia it increased to within the normal range after an oral dose of 500 μg. (in one patient after 1,000 μg.), while after 3,000 μg. a marked rise in serum level occurred in 5 out of 6 patients. A rise in erythrocyte count and haemoglobin level occurred when the serum vitamin-B_{12} level was increased, but was suboptimal with doses of less than 3,000 μg. by mouth. Urinary excretion of the vitamin after an oral dose of 3,000 μg. corresponded approximately to that following an intramuscular dose of 10 μg., but was not affected by smaller doses. No significant difference was noted between normal subjects and patients with macrocytic anaemia in the urinary excretion of vitamin B_{12} after oral administration [a finding which differs from that of workers in Great Britain]. No correlation was observed between the maximum total serum vitamin-B_{12} activity and the haematopoietic response.

The authors point out that the differences between their findings and those of others reported in the literature may well be associated with differences in the assay technique used. *Janet Vaughan*

135. **Intrinsic Factor Studies. II. The Effect of Gastric Juice on the Urinary Excretion of Radioactivity after the Oral Administration of Radioactive Vitamin B_{12}**
R. F. SCHILLING. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **42**, 860–866, Dec., 1953. 2 figs., 17 refs.

It has been shown that small doses of vitamin B_{12} given by mouth have no appreciable effect on urinary excretion of the vitamin. In this paper from the University of Wisconsin Medical School the author describes experiments in which 6 normal subjects and 6 patients with pernicious anaemia in remission were given an oral dose of 2 μg. of radioactive vitamin B_{12} (cyanocobalamin), together with 1,000 μg. of non-radioactive vitamin B_{12} by subcutaneous injection, the radioactivity of the urine then being determined at intervals. In normal subjects there was appreciable radioactivity in the urine passed within a few hours of ingestion of the vitamin, whereas the patients with pernicious anaemia showed no appreciable radioactivity in their urine. When the radioactive cyanocobalamin was given with normal gastric juice the urine became radioactive, but if the gastric juice was first boiled, the urine was not radioactive. No radioactivity was noted in the serum. From the fact that a subcutaneous " flushing " dose

of non-radioactive vitamin B_{12} made radioactivity appear in the urine, the author presumes that this radioactivity represents vitamin B_{12} or a closely related metabolite, and suggests that these findings support Castle's theory that intrinsic factor enhances the intestinal absorption of vitamin B_{12} in patients with pernicious anaemia. They may also provide a new method for the study of the intrinsic factor, since observations can be made on patients with pernicious anaemia in remission.

Janet Vaughan

BLOOD-GROUP SEROLOGY

136. **Cortisone and Erythroblastosis. Evaluation of Management of Pregnancy in the Rh-immunized Woman** E. J. DeCosta, A. B. Gerbie, and E. L. Potter. *Obstetrics and Gynecology* [*Obstet. Gynec.*] **3**, 131–140, Feb., 1954. Bibliography.

The literature of Rh-immunization is reviewed. About 15% of American white women are Rh negative and some 13% marry Rh-positive men, but erythroblastosis foetalis occurs in not more than 0·5% of the offspring of these marriages. Mild cases of erythroblastosis require little or no treatment, but moderate to severe cases usually need immediate exchange transfusion. In the most serious cases, intra-uterine foetal death occurs, precluding any postnatal treatment.

In view of the benefit claimed for the use of cortisone in pregnant iso-immunized, Rh-negative women, this hormone was tried in 8 cases at the Chicago Lying-in Hospital. Only 2 babies survived, and one of these was Rh negative, although its mother's anti-Rh titre rose during pregnancy from 10 to 40. The other baby survived after two exchange transfusions; the mother of this child had received cortisone for only 16 days, during which time the antibody titre rose from 32 to 128. Two of the remaining babies were born alive, but were hydropic and lived less than one hour. The remaining 4 infants were stillborn, although cortisone had been given to these mothers for 35 to 124 days in doses up to 150 mg. per day.

The theoretical reasons for the administration of cortisone to Rh-immunized mothers are discussed. The chances of maternal immunization arising are said to be less than 5% in Rh-negative women with positive husbands, but once immunization has occurred, all subsequent Rh-positive infants are affected. Often the severity of the erythroblastotic process increases with succeeding pregnancies, though not always. Homozygous males appear to beget infants whose blood is more potent antigenically.

At the Chicago Lying-in Hospital the survival rate of erythroblastotic babies born to women who had previously had an affected baby ranged from 35 to 44%. The titre in the early part of pregnancy is of considerable significance. For example, a low titre of antibodies arising late during a pregnancy is generally associated with a mildly affected baby, whereas a high titre of antibodies early in pregnancy is associated with a severely affected infant. A terminal rise in titre is sometimes an unfavourable sign. However, foetal erythroblastosis does occur in babies of mothers with low and even falling titre.

The authors conclude that administration of cortisone to Rh-negative immunized women does not influence antibody titre or the survival rate of affected babies. The development of acute (mild) pre-eclamptic toxaemia was observed in one patient receiving cortisone. They end by pointing out that without any special preventive therapy a successful outcome of pregnancy can be expected in 35% of immunized mothers who have previously had an erythroblastotic baby which was stillborn or died soon after birth, and that excluding Rh-negative babies, infant survival in such cases can be expected to be about 24% if the baby receives prompt and adequate treatment. *John Murray*

137. **Rh Iso-immunization. Treatment or Prevention** H. L. Gainey, K. S. Nicolay, J. E. Keeler, and M. E. Doyle. *Obstetrics and Gynecology* [*Obstet. Gynec.*] **3**, 141–149, Feb., 1954. 24 refs.

The authors believe that the incidence of iso-immunization in Rh-negative mothers can be appreciably reduced by more careful management of the patient. With this object in view, the records of 50 iso-immunized women seen in private practice in Kansas City were investigated in retrospect, a comparable group of non-immunized Rh-negative women with homozygous Rh-positive husbands being subjected to a similar scrutiny. No correlation between increase in titre of antibody and outcome of pregnancy was observed, but the authors did note that the later in pregnancy the antibody appeared, the better the prognosis for the infant.

Of the 50 immunized women, one had been immunized by blood transfusion and had never been pregnant, while 3 were primipara with negative histories who in due course were delivered of normal babies. Of the remaining 46 mothers, 27 (58%) gave a history suggestive of "induced pathology", by which is meant that some had received transfusion of incompatible blood, while others had been subjected to doubtfully necessary obstetrical interference before or at labour. Of the non-immunized women, only 7% showed any evidence of "induced pathology" in their histories. The authors conclude that obstetricians should take more care of Rh-negative women, and in particular avoid any traumatic manœuvre which might upset the placental blood barrier. *John Murray*

138. ***ABO* Groups in Blood Platelets** J. Gurevitch and D. Nelken. *Nature* [*Nature* (*Lond.*)] **173**, 356, Feb. 20, 1954. 1 ref.

Platelet suspensions freshly prepared from 40 different specimens of blood, with precautions against spontaneous agglutination, were tested against their own serum and sera of Groups A, B, AB, and O. No agglutination occurred with AB serum or with their own serum, but with the other antisera agglutination occurred in accordance with the agglutination reactions of the corresponding erythrocytes. *I. Dunsford*

Respiratory System

139. **Preclinical Bronchogenic Carcinoma**
K. R. BOUCOT and M. J. SOKOLOFF. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **69**, 164–172, Feb., 1954. 9 refs.

In this paper from the Department of Public Health, Philadelphia, the authors discuss the incidence of cases of bronchogenic carcinoma among patients attending two mass radiography units and then review the 77 cases diagnosed. The incidence in 142,156 subjects for whom complete records were available was 30 per 100,000. Age and sex were significant factors; the disease was 55 times more frequent in subjects over 45 years of age than in those under 45, and the ratio of affected males to females was rather more than 10:1. There was no difference between white and coloured subjects in the incidence of the disease.

Only 7 of the 77 patients were truly asymptomatic; 43 believed they were well, but symptoms were elicited in response to careful questioning, and 27 were ill enough to consult a doctor. Cough was the most frequent symptom, followed by loss of weight, pain in the chest, sputum, haemoptysis, dyspnoea, fatigue, fever, and chills, in that order. It was found that 11 patients with haemoptysis had not sought medical advice. In 22 cases earlier radiographs which had been considered normal were re-examined; in 11 of these the appearances were "definitely abnormal". There were 6 cases of concurrent active tuberculosis with positive sputum. The tumours were classified as follows: squamous-cell carcinoma (45 cases), adenocarcinoma (11 cases), undifferentiated carcinoma (17 cases), and unspecified (4 cases). Resection was performed in 22 cases, 14 of the patients being alive 1 to 6 years after operation, compared with only 6 of the 55 patients not operated on.

The authors do not consider that mass radiography is adequate when symptoms are present; in symptomless cases, however, radiography should be carried out every 6 months, especially on men over 45 years of age.

I. Ansell

140. **Pulmonary Function in Cystic Fibrosis of the Pancreas**
J. R. WEST, S. M. LEVIN, and P. A. DI SANT' AGNESE. *Pediatrics* [*Pediatrics*] **13**, 155–164, Feb., 1954. 2 figs., 23 refs.

Tests of pulmonary function were carried out on 6 patients aged between 12 and 15 years with cystic fibrosis of the pancreas. In all cases steatorrhoea had begun in infancy, there was complete absence of tryptic activity in the duodenal contents, and there was a long history of pulmonary infections of varying severity: in 4 cases recurrent bronchopneumonia had resulted in chronic dyspnoea and wheezing, clubbing, and cyanosis.

The abnormalities demonstrated in pulmonary function roughly paralleled the degree of clinical disability. The vital capacity was reduced in 3 cases and the residual volume (expressed as a percentage of total lung volume) in 4 cases, while the index of intrapulmonary mixing was abnormal in 5 cases. The maximum breathing capacity was significantly reduced in 3 cases. There was gross arterial oxygen unsaturation (76%) and a high arterial carbon dioxide tension (69 mm. Hg) in the worst case, in which subsequent necropsy showed the presence of cor pulmonale.

There was no abnormality in the total pulmonary ventilation of these patients, nor of diffusion of gases across the alveolo-capillary membrane, and the authors consider that pulmonary dysfunction was due to the grossly uneven ventilation of different parts of the lungs, due perhaps to partial occlusion of some bronchi by secretions. This functional defect is similar to that seen in chronic pulmonary emphysema from other causes. The authors emphasize that in some cases the pulmonary symptoms can be greatly alleviated by intensive antibiotic treatment.

W. A. Briscoe

141. **Determination of Total Lung Capacity in Disease from Routine Chest Roentgenograms**
S. COBB, D. J. BLODGETT, K. B. OLSON, and A. STRANAHAN. *American Journal of Medicine* [*Amer. J. Med.*] **16**, 39–54, Jan., 1954. 4 figs., 31 refs.

The authors claim that the volume of air in the lungs can be estimated with a fair degree of accuracy from routine radiographs taken in full inspiration, the "radiological chest volume" (R.C.V.) being determined by multiplying the area of the lungs and mediastinum, as measured with a planimeter on the postero-anterior film, by the horizontal diameter of the chest measured on the lateral film. The R.C.V. thus calculated was compared with the total lung capacity as measured by the nitrogen wash-out method in 76 patients suffering from emphysema, carcinoma, tuberculosis, and other pulmonary diseases at Albany Hospital, Albany, New York. In patients with emphysema or after pneumonectomy or lobectomy the R.C.V. was greater than the total lung capacity but was closely correlated with it (correlation coefficient 0·906), and a regression equation is given whereby the latter may be derived from the former in such cases. In cases where lung tissue was replaced by masses of non-functioning material the correlation between R.C.V. and total lung capacity was not so close, and it is suggested that the degree of replacement of functioning tissue in the individual patient can be estimated quantitatively from the difference between the two values.

The index $\frac{\text{Residual Volume}}{\text{Total Lung Capacity}} \times 100$ was determined in 17 cases of emphysema, the total lung capacity being determined both by derivation from the R.C.V. and

also by conventional spirometric methods, and the residual volume being calculated by subtracting the vital capacity (measured spirometrically) from the total lung capacity in each case. The resultant indices agreed to within $\pm 10\%$ in 16 of the 17 cases. Agreement was almost as good in cases of bronchogenic carcinoma when allowance was made for the diseased areas in determining the R.C.V., but agreement was poor in other conditions. It is suggested that by a combination of simple spirometry and measurements made on routine *x*-ray films large numbers of individuals could be screened for " abnormal changes in pulmonary compartment ratios ".

W. A. Briscoe

142. **Spirometric Analysis of Lung Function following Pulmonary Resection in Childhood**

J. A. TURNER. *Pediatrics* [*Pediatrics*] **13**, 17–23, Jan., 1954. 2 figs., 14 refs.

Longacre *et al.* and Bremer (*J. thorac. Surg.*, 1937, **6**, 237 and 336) showed that tissue regeneration took place in the alveoli of the remaining lung after pneumonectomy in puppies, in contrast to the mere dilatation found in adult dogs. This finding led the former authors to postulate that the earlier resection of the lung was performed in children, the less would be the impairment of cardio-respiratory function.

In the present paper the author presents the results of an investigation, carried out at the University and the Hospital for Sick Children, Toronto, of lung function in 40 individuals who had undergone pulmonary resection in childhood. The patients (24 female and 16 male) ranged in age from 8 to 24 years, 20 being over 15 and 20 under 15 at the time of study. The operation had been performed from 3 months to 19 years earlier, the patients being then aged from 3 to 15 years, and a suppurative process had been the indication for surgery in all cases. At the re-examination, as well as note being taken of subjective symptoms such as cough and dyspnoea, a clinical and radiological examination of the chest was made, and measurements of resting ventilation, oxygen consumption, average tidal air, vital capacity, and maximum voluntary ventilatory capacity were estimated from the findings obtained on at least four occasions. These results were compared with the predicted normal levels for each patient.

Vital capacity was found to be reduced in proportion to the amount of lung removed, this finding being particularly clear in patients subjected to bilateral resection. In all but 9 cases there was a more obvious reduction in the inspiratory than in the expiratory fraction of vital capacity. In a previous investigation the author, with McLean, (*Pediatrics*, 1951, **7**, 360) had shown that in cases of suppurative lung disease the preoperative reduction of vital capacity was mainly in the expiratory reserve. In view of this, the 9 postoperative cases in the series showing reduced expiratory reserve were investigated for residual disease, and in 7 cases evidence of such disease was found. In all cases the maximum breathing capacity was reduced below the predicted level. There was a fairly close correlation between the degree of reduction in maximum breathing capacity and the development of postoperative emphysema, the latter being most marked in a group of 3 patients subjected to bilateral resection, whose maximum breathing capacity was below 40% of the predicted normal. There was only one case of significant reduction in breathing reserve (an indication of dyspnoea in the subject tested), and this patient was dyspnoeic even at rest. In all the other cases breathing reserve was well within normal limits.

From his results the author draws the conclusion that these tests broadly reflect the extent of pulmonary resection and the degree of development of postoperative emphysema, and that these two factors, and not the patient's age at the time of operation, are the decisive ones in the determination of the degree of resulting pulmonary function. He is therefore unable to confirm the postulate of Longacre *et al.* mentioned above.

A. M. Macarthur

143. **Metaplasia and Dyskeratosis of Bronchial Epithelial Cells following Inhalation of Trypsin and Desoxyribonuclease**

S. M. FARBER, S. L. PHARR, H. F. TRAUT, D. A. WOOD, and R. D. GORMAN. *Laboratory Investigation* [*Lab. Invest.*] **3**, 33–38, Jan.–Feb., 1954. 3 figs., 6 refs.

In this paper from the Cancer Research Institute and the University of California School of Medicine, San Franciso, the authors draw attention to the rapid development of cytological changes in the bronchial epithelium of patients receiving inhalations of trypsin and desoxyribonuclease. Trypsin, dissolved in Sorensen's buffered phosphate solution, was administered to 24 patients with moderate or severe pulmonary tuberculosis, all of whom were producing large quantities of sputum. The usual dose was 100,000 to 150,000 units daily, and the treatment was generally given for an average period of 10 days. No significant clinical benefit was observed.

Desoxyribonuclease, 2 to 5 mg. daily, was then added to the trypsin for periods ranging from 4 to 11 days in 16 cases, and a reduction in the cough was noted in 9 cases and reduced viscosity of sputum in 11. More than half the patients, however, developed reactions to the treatment, including sore throat, renewed increase in the cough, aphonia, and haemoptysis, and in some cases a sensitivity reaction. Cytological studies carried out on the sputum showed that the enzymes had little or no effect on the leucocytes, macrophages, or fibrin present. But in 12 of the 16 cases changes were seen in the epithelial cells, the most common feature of which was the appearance of numerous atypical metaplastic cells containing large, hyperchromatic nuclei, in which the chromatin was distributed in irregular clumps, and there were also occasional multinucleated cells. In addition, dyskeratosis of the exfoliated cells was observed, the cells showing large, immature nuclei lying in a more mature cytoplasm. The occurrence of dyskeratosis is not generally associated with chronic pulmonary disease. The authors stress that these changes did not cease when the inhalation of the enzymes was stopped, but in fact have persisted and in most cases have increased in the 6 months since cessation of the treatment. They

suggest that further animal studies on the effects of these enzymes, particularly on the epithelium of the respiratory tract, should be carried out. *B. Nordin*

INFLAMMATORY DISEASES OF THE LUNG

144. *Hemophilus influenzae* Bacillus in Viral Pneumonias

L. C. GABRIELSEN, D. O. LYNN, and C. L. LEEDHAM. *Diseases of the Chest* [*Dis. Chest*] **25**, 206–214, Feb., 1954. 15 refs.

During an epidemic of primary atypical pneumonia at a U.S. Army Station in Hawaii the authors noticed that those of their patients whose sputum contained *Haemophilus influenzae* (presumably as secondary invaders) tended to have a more severe illness than those with a normal bacterial flora. Among 300 consecutive and comparable cases there were 41 in the former group and 259 in the latter.

The average stay in hospital for the group with *H. influenzae* was 16·7 days, whereas in the control group the figure was 11·6 days. On the average the temperature rose higher and fever was of longer duration in the former group. No significant differences were detected by *x*-ray examination in degree of localization or rapidity of resolution of the consolidated areas. Relapses occurred in 19·5% of cases with *H. influenzae* infection compared with 1·5% of the control group. The authors record their impression that in cases infected with *H. influenzae* chloramphenicol or aureomycin (2 g. daily) was of benefit, whereas penicillin (300,000 to 600,000 units daily) was not. There was, however, no radiological evidence in support of this.

[The value of this paper is difficult to assess as laboratory evidence supporting the diagnosis of primary atypical pneumonia is not provided.] *K. Zinnemann*

145. Chemotherapy of Primary Atypical Pneumonia

G. MEIKLEJOHN, W. G. THALMAN, D. J. WALIGORA, C. H. KEMPE, and E. H. LENNETTE. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **154**, 553–557, Feb. 13, 1954. 8 refs.

The relative value of penicillin, aureomycin, oxytetracycline (" terramycin "), and chloramphenicol in the treatment of primary atypical pneumonia is discussed with reference to a series of 149 patients treated at a U.S. Army station hospital between October, 1950, and March, 1951. [The criteria for the diagnosis are not given and the titres of cold haemagglutinins are not recorded.] Patients with bacterial or influenzal pneumonia were excluded, as were those with a temperature below 100° F. (37·8° C.) and those in whom spontaneous recovery was imminent. [Patients with segmental aspiration pneumonia were not sought and so not excluded, which casts some doubt on the value of the authors' statistical analysis of their results.]

In general, when the temperature was below 102° F. (38·9° C.) there was an equally good response to each of the four antibiotics used, but in cases in which the temperature exceeded 103° F. (39·4° C.) the response to aureomycin, oxytetracycline, and chloramphenicol was better than that to penicillin. *D. Geraint James*

146. Pneumococcal Lobar Pneumonia Treated with One Injection of Dibenzylethylenediamine Dipenicillin G. A Report of 49 Cases

I. C. WALKER and M. HAMBURGER. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **4**, 76–82, Jan., 1954. 2 figs., 15 refs.

It has been shown that the release of dibenzylethylenediamine dipenicillin G from its muscular depot is so slow that measurable levels are present in the blood 10 to 14 days after one injection of 600,000 units. This preparation was tried in the treatment of 49 cases of pneumococcal lobar pneumonia at Cincinnati (Ohio) General Hospital. Clinical diagnosis was confirmed by *x*-ray examination of the chest, estimation of the blood count, analysis of the urine, and culture of specimens of blood and sputum. If there was no improvement in the clinical condition 48 to 96 hours after the injection, aqueous benzylpenicillin was substituted. There were no deaths in the series.

In 14 of 19 patients given one injection of 600,000 units the results were good, the average time taken for the temperature to fall to and remain at 100° F. (37·8° C.) or lower being 81 hours; 4 patients required additional treatment, while one was " a probable failure ". One injection of 1,200,000 units was given to 30 patients, 22 of whom required no additional therapy, the temperature usually falling to normal within 44 hours. Treatment was " partially unsuccessful " in 3 and a failure in 5 of the remaining 8 cases in this group.

In the majority of cases the concentration of penicillin in the blood was 0·05 μg. per ml. or higher 4 hours to 10 days after injection, regardless of whether 600,000 or 1,200,000 units had been given. No sensitivity reactions were observed. The failures could not be related to the age of the patient, the type of pneumococcus, the dosage employed, or to the blood level of penicillin, which was within the " therapeutic " range in both successful and unsuccessful cases.

The authors conclude that while dibenzylethylenediamine dipenicillin G is adequate in the treatment of many cases of pneumococcal pneumonia, it cannot be recommended for routine use in all. *D. J. Pearce*

147. Acute Respiratory Infections in Emphysema. An Account of 118 Cases

T. SIMPSON. *British Medical Journal* [*Brit. med. J.*] **1**, 297–301, Feb. 6, 1954. 1 fig., 26 refs.

In the author's experience, emphysema complicated by acute respiratory infection is not an uncommon medical emergency. Moreover, the prognosis is grave; of 118 patients with emphysema and acute respiratory infection admitted to Chase Farm Hospital, Enfield, Middlesex, between March, 1947, and May, 1952, 41 died in hospital and 34 died within 21 months of discharge. The author points out that papilloedema develops in some cases during the phase of acute infection; this was observed

in 8 of his cases. Discussing treatment he emphasizes that coma and cerebral symptoms often follow administration of oxygen. Oxygen given in a tent in cases of hypoxia may precipitate coma owing to retention of carbon dioxide; this risk is reduced if oxygen is first given by nasal catheter or by Tudor Edwards nasal spectacles, a tent being used when the patient is acclimatized to a high concentration of oxygen. Breathing exercises and administration of antispasmodics are advised in the after-care of these patients. At necropsy, which was performed in 41 cases, severe bronchiolitis, emphysematous lungs, and right ventricular hypertrophy were found. In 4 cases a marked cerebellar pressure cone was observed. *J. Robertson Sinton*

148. **Lung Abscess and Bronchial Catheterization**
H. METRAS and J. CHARPIN. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **27**, 157–172, Feb., 1954. 10 figs., bibliography.

Catheterization of segmental bronchi was performed in 51 cases of simple lung abscess. This procedure has two main advantages: (1) it facilitates bronchography because the medium enters the abscess cavity, a result which is not usually achieved with other methods; and (2) it permits accurate local instillation of an antibiotic. The authors used semi-stiff rubber catheters of various shapes, which were introduced under fluoroscopy after local anaesthesia had been induced. The procedure was well tolerated. Usually the antibiotic was instilled by means of the catheter on 6 to 8 occasions in each case, contrast radiographs being taken before and after treatment. The authors point out that residual small cavities, which are common, may not be seen on plain films and tomograms, but that these cavities often close spontaneously in the ensuing months.

Of the authors' series, which included cases of chronic and multiple lesions, healing occurred in 37. In 14 the treatment was a failure and resection, which is advised in such cases, was carried out in 9. *S. F. Stephenson*

149. **Changing Trends in the Treatment of Lung Abscess**
D. H. WATERMAN and S. E. DOMM. *Diseases of the Chest* [*Dis. Chest*] **25**, 40–53, Jan., 1954. 1 fig., 19 refs.

While admitting that the use of antibiotics has profoundly influenced the prognosis in cases of lung abscess, the authors attempt to show, from a review of 218 personal cases seen between 1941 and 1952, that medical and surgical procedures are complementary in the treatment of this condition. During the period a total of 401 cases of lung abscess came under the authors' care; in 218 (54·4%) of these, which form the basis of this report, primary lung abscess or suppurative pneumonia was present; of the remainder, carcinoma with suppuration was present in 174, adenoma with suppuration in 3, and embolic abscess with pyaemia in 6. It is stated that in 1941 carcinoma was an aetiological factor in only 11% of cases, but that by 1948 this figure had risen to 52%

Of the 218 patients with primary lung abscess, 83 were treated, before antibiotics were generally available, with rest in bed, administration of sulphadiazine, and postural drainage, surgery being carried out if improvement was not prompt and steady. Drug therapy in the remaining 135 cases included penicillin by intramuscular injection in a dose of 100,000 to 300,000 units every 3 hours, penicillin aerosol in a dose of 25,000 to 50,000 units every 3 hours, and, later, aureomycin and chloramphenicol by mouth and oxytetracycline aerosol. The most effective of these was penicillin by intramuscular injection or as an aerosol.

Treatment was conservative in 134 cases, in 60 of which no antibiotics were given, but the morbidity rate was 29% and the death rate 12·7%. Open drainage was required in 36 cases (in 16 of which no antibiotic had been given), but the condition became chronic in 8 and proved fatal in 5. Lobectomy, segmental lobectomy, or (rarely) pneumonectomy was performed in 55 cases, the morbidity rate here being 5% and the mortality 9%. A comparison of the results in the three groups before and after antibiotics became available clearly demonstrated the value of this additional form of therapy.

The authors emphasize the danger that lies in the use of antibiotics, leading as it does in some cases to a delay in diagnosis, and the need for bronchoscopy in all cases of lung abscess. They conclude that although the results of surgical treatment are better than the results of conservative treatment, the two are "complementary rather than competitive". *C. A. Jackson*

PULMONARY EMPHYSEMA

150. **Raised Intracranial Pressure in Emphysema**
E. K. WESTLAKE and M. KAYE. *British Medical Journal* [*Brit. med. J.*] **1**, 302–304, Feb. 6, 1954. 3 figs., 12 refs.

The cause of papilloedema occurring during acute respiratory infection in patients with emphysema was studied at Chase Farm Hospital, Enfield, Middlesex.

Lumbar puncture was performed on 8 such patients immediately after admission to hospital and on 4 after 4 to 80 hours of oxygen therapy. In 10 of the patients the cerebrospinal-fluid pressure was above the upper limit of normal (200 mm. H_2O), being over 350 mm. in 5. Arterial anoxaemia was present in all and hypercapnia in all except one. In a non-emphysematous subject an increase in intracranial pressure was induced by the inhalation of mixtures with either high carbon dioxide or low oxygen content. The authors suggest that the mechanism of the rise in pressure is probably the cerebral vasodilator effect of anoxia with carbon dioxide retention. *J. Robertson Sinton*

151. **Ventilatory Response to Carbon Dioxide in Pulmonary Emphysema**
S. M. TENNEY. *Journal of Applied Physiology* [*J. appl. Physiol.*] **6**, 477–484, Feb., 1954. 6 figs., 19 refs.

The response to inhalation of carbon dioxide was studied at the University of Rochester School of Medicine, Rochester, New York, in 5 normal subjects, 15 patients with emphysema, one patient with metabolic alkalosis due to prolonged gastric lavage, and one patient with metabolic acidosis due to the prolonged ingestion of

ammonium chloride. Resting measurements were made while the subject breathed 100% oxygen (to eliminate any anoxic stimulus) for 15 minutes, and again while mixtures containing 3·3% and 4·7% carbon dioxide in oxygen were administered, each for 15 minutes. The plasma carbon dioxide content was determined in samples of venous blood collected under oil.

The results confirm the observation that in patients with emphysema inspired carbon dioxide is less effective than usual in increasing ventilation. But when the blood bicarbonate content was reduced by the administration of the carbonic anhydrase inhibitor, "diamox", in doses of 24 mg. per kg. body weight per day, the ventilatory response of the emphysematous subjects to inspired carbon dioxide increased. Similarly the response of the patient with metabolic alkalosis, which was reduced initially, increased as the plasma bicarbonate level fell on discontinuing the gastric lavage, while that of the patient with metabolic acidosis, which was more than normal initially, fell towards normal as his plasma bicarbonate level rose with the omission of ammonium chloride.

All these findings are compatible with the general rule that the higher the plasma bicarbonate level, the lower the ventilatory response to inspired carbon dioxide, and vice versa. The author points out also that the higher the plasma bicarbonate level, the greater the buffering power of the blood and the smaller will be the rise in arterial *p*H due to the inspiration of carbon dioxide.

W. A. Briscoe

152. **The Relationship of Arterial Hypoxemia to Disability and to Cor Pulmonale with Congestive Failure in Patients with Chronic Pulmonary Emphysema**

R. D. MILLER, W. S. FOWLER, and H. F. HELMHOLZ. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **28**, 737–743, Dec. 30, 1953. 7 refs.

The authors set out to determine the relation of a low oxygen content in the arterial blood in chronic pulmonary emphysema both to the disability caused and to the presence of right heart failure. For this purpose, the clinical records of 240 cases of pulmonary emphysema seen at the Mayo Clinic in recent years were reviewed. In every case the arterial oxygen saturation had been recorded at rest (and in most cases also during exercise or on standing) by ear oximeter with a continuous photokymographic recording.

The cases were first divided into three groups according to disability (that is, to the degree of dyspnoea) without knowledge of the oxygen saturation values. They were then redistributed into three other groups according to the results of the oximeter studies, the first group containing those with normal arterial oxygen saturation values both at rest and on exercise, the second those with a normal value at rest which fell by more than 2% on exercise, and a third group those with hypoxaemia at rest. Comparison of the two sets of groups showed that, in general, the incidence of hypoxaemia was greater in the more dyspnoeic patients. However, in the group with the mildest disability one-sixth of the patients were hypoxaemic at rest and a further sixth became hypoxaemic on exertion. In contrast, one-third of the patients with the most severe dyspnoea had normal arterial oxygen saturation, even after exercise to the limit of tolerance. No relationship was found between the presence of a productive cough and the occurrence of hypoxaemia.

It was considered that hypoxaemia played an important part in the development of cor pulmonale with congestive failure. Of 122 patients with transient or persistent hypoxaemia, 18 had evidence of right heart failure, compared with only one patient out of 118 with normal arterial oxygen saturation.

The authors conclude that arterial hypoxaemia is not closely correlated with the severity of the dyspnoea in patients with chronic pulmonary emphysema, but that it is related to the development of cor pulmonale with congestive failure.

Keith Ball

153. **Treatment of Pulmonary Emphysema with Aerosolized Bronchodilator Drugs and Intermittent Positive-pressure Breathing**

W. S. FOWLER, H. F. HELMHOLZ, and R. D. MILLER. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **28**, 743–751, Dec. 30, 1953. 15 refs.

Previous methods advocated for the treatment of pulmonary emphysema are briefly recapitulated. None has proved entirely satisfactory. At the Mayo Clinic, therefore, the effectiveness of intermittent positive-pressure breathing (I.P.P.B.) of oxygen in cases of chronic pulmonary emphysema was assessed, since good results have been claimed for this treatment.

A total of 41 patients with chronic diffuse pulmonary emphysema were divided into three groups and treated in the following ways. (1) To the first group oxygen was administered by I.P.P.B. for 20 minutes 4 times daily for 12 days, an inspiratory pressure of 15 to 20 cm. of water being used. No significant improvement occurred in this group. (2) The second group was given oxygen by I.P.P.B. with the addition of *iso*propylnoradrenaline (isoprenaline) as an aerosol. In this group 14 out of 20 patients noticed improvement. (3) In the third group, isoprenaline given by I.P.P.B. was found to give no better results than when it was administered without using positive pressure. On the patients receiving oxygen and isoprenaline (with or without I.P.P.B.) various pulmonary function tests, including those for vital capacity, maximum breathing capacity, total lung volume, and arterial oxygen saturation were carried out at rest and after exertion. No significant change in any of these values was found after 1 to 2 weeks' treatment with oxygen–isoprenaline. On the other hand, an increase of about 20% both in vital capacity and maximum breathing capacity was found immediately after an inhalation of oxygen and isoprenaline.

It is concluded that moderate symptomatic improvement can be obtained in pulmonary emphysema by giving oxygen with an aerosol of isoprenaline, whether or not the oxygen is administered at intermittent positive pressure. The lack of improvement in the results of the pulmonary function tests indicates that no alteration of the underlying pulmonary lesion was achieved.

Keith Ball

Otorhinolaryngology

154. **On the Indication of the Conservative Radical Mastoidectomy.** [In English]
R. M. VERSTEEGH. *Acta oto-laryngologica* [*Acta oto-laryng. (Stockh.)*] **43**, 642–647, Dec., 1953. 4 figs., 6 refs.

In this dicussion of the treatment of chronic otitis the author points out that when a diseased incus is found at operation and removed, there is seldom an improvement in hearing. When the incus is intact and left in position, however, the subsequent improvement in hearing may be enough to allow conversation to be heard. Patients with good hearing who require a mastoid operation for chronic infection should be treated without delay, for the incus will be found to be normal and hearing will be preserved; but if operation is postponed until the hearing is poor, the incus will be affected by the disease and no improvement in hearing can be expected.

William McKenzie

155. **Therapy of Acute Purulent Otitis Media with Dibenzylethylenediamine Dipenicillin G**
S. H. WALKER. *Journal of Pediatrics* [*J. Pediat.*] **44**, 50–54, Jan., 1954. 7 refs.

The author reports the results obtained at Fort Meade Army Hospital, Maryland, with a single injection of dibenzylethylenediamine dipenicillin G, with or without a single injection of 300,000 units of procaine benzylpenicillin, in the treatment of acute purulent otitis media. Of 100 patients in the series, 49 received both drugs and 51 received a single injection of dibenzylethylenediamine dipenicillin G only. In both groups the alleviation of signs and symptoms was comparable to that to be expected from any available form of treatment.

With few exceptions patients in both groups were asymptomatic in 48 hours. The response in patients who received both drugs did not appear to differ significantly from that in patients receiving dibenzylethylenediamine dipenicillin G only. The author therefore concludes that the latter drug is adequate in the treatment of purulent otitis media, although he notes that sensitivity reactions, when these occurred, were prolonged, and that in a number of cases there was local pain at the site of injection. This form of penicillin was, however, effective against pharyngeal lymphoid hypertrophy.

E. D. Dalziel Dickson

156. **The Treatment of Severe Progressive Epistaxis by Radiotherapy**
J. P. STEWART and J. D. SAMMON. *Journal of Laryngology and Otology* [*J. Laryng.*] **68**, 82–91, Feb., 1954. 6 figs., 9 refs.

Cases of epistaxis severe enough to be referred to hospital for treatment appear to have increased in frequency in recent years. The number of such cases treated annually in out-patients at the Edinburgh Royal Infirmary rose progressively from 110 in 1944 to 200 in 1952, while the number of admissions for the same condition rose from 16 in 1948 to 32 in 1952. In this paper the authors describe the treatment by radiotherapy of 7 men and one woman whose ages ranged from 30 to 69 years. The bleeding was in each case from Little's area on the septum. The haemoglobin level on admission varied between 30 and 60%, and 5 of the patients required transfusion before radiotherapy.

In order to minimize the skin reaction on the face, standard high-voltage *x*-ray equipment was used at 240 kV and 15 mA, with a half-value layer of 2·5 mm. Cu. In most cases two directly opposed lateral fields 6×6 cm. covering the entire nasal cavity were treated each day, the eyes and lips being shielded with lead, and any air space between the two fields being packed with bolus. A minimum central dose of 2,000 r was given in one week, the maximum skin dose averaging 2,500 r.

In each case the bleeding ceased before the completion of treatment and has not recurred. [The histological effects, as seen in biopsy specimens of treated mucosa, are fully described and illustrated.]

Norman W. MacKeith

157. **One-stage Radical Resection of Cervical Oesophagus, Larynx, Pharynx, and Lateral Neck with Immediate Reconstruction**
J. J. CONLEY. *Archives of Otolaryngology* [*Arch. Otolaryng. (Chicago)*] **58**, 645–654, Dec., 1953. 11 figs.

The advantage of the one-stage operation for cancer of the pharynx, hypopharynx, postcricoid areas, and cervical oesophagus is that the action of saliva on the wound, with the risk of infection and of enzyme action on the skin flaps, is entirely eliminated. The author advocates a radical resection, closing the gap between the pharynx and oesophagus with free, thick-split skin grafts, covered above by the prevertebral fascia and skin flaps of the neck and below by the lobes of the thyroid gland. To prevent postoperative contracture the restored pharyngo-oesophageal tube is built up around a wire-mesh or plastic stent, which should be left *in situ* for 6 months after operation.

The operation is not suitable in heavily irradiated cases or as a method of reconstruction when there has been severe postoperative infection, the chief indication being extensive carcinoma, especially where block dissection of the neck is needed. The author considers that "in general, in surgery of the pharynx it is impractical to retain the larynx when it has been necessary to sacrifice the superior laryngeal nerves, epiglottis, and more than half of the hyoid bone. When these three anatomical elements are destroyed or eliminated in the surgical process, even though the patient still has the ability to use the larynx as an organ of phonation, it is usually impossible for him to carry on normal deglutition without the serious complications associated with frequent aspiration of saliva, food and drink". The operation has been performed successfully 6 times in the last 2 years.

F. W. Watkyn-Thomas

Urogenital System

158. **Prognosis and Treatment of Anuria of Tubular Origin in 226 Cases.** (Pronostic et traitement des néphropathies tubulaires anuriques. A propos de 226 cas)
M. DÉROT and M. LEGRAIN. *Bulletin de l'Académie nationale de médecine* [*Bull. Acad. nat. Méd. (Paris)*] **138**, 37–40, Jan. 19, 1954.

The authors present a short summary of their observations on 226 patients suffering from acute nephrosis with anuria or oliguria admitted, in some cases *in extremis*, to the Hôtel-Dieu, Paris, during the years 1948–53. Of these patients 115 had developed renal failure after abortion, of whom 87 (76%) recovered and 28 died; 21 became anuric after blood transfusion, of whom 8 (38%) recovered and 13 died; 21, of whom 5 (24%) recovered and 16 died, were anuric after a surgical operation; of 18 suffering from mercury poisoning, 14 (78%) recovered and 4 died; of 6 patients with carbon tetrachloride poisoning, all recovered; of 3 with sodium chlorate poisoning, 1 died; and of 4 with sulphonamide poisoning all recovered; yet of 7 with combined renal and hepatic damage, all died. Lastly, among 3 patients with biliary-tract lesions and haemoglobinuria there were 2 deaths, and of 28 with anuria of unspecified origin, 13 recovered (46%) and 15 died.

The authors conclude that uncomplicated anuria has a fairly good prognosis as regards restitution of function. The serum urea level was found to be a reliable guide in that respect; if values remained below the level of 400 mg. per 100 ml., purely medical treatment was usually successful, but pyrexia, advanced age, and hyperpotassaemia made a favourable outcome less likely. In the experience of the authors no one particular line of treatment stood out as being of more value than any other; in 105 of the 226 cases a restricted fluid intake, a bland diet supplying 2,000 Cal., infusions of 500 ml. of 20% glucose, electrolyte replacement according to individual requirements, and administration of exchange resin in cases of hyperpotassaemia were sufficient to enable the patient to regain full renal efficiency, as judged at a 5-year follow-up examination. Extrarenal elimination of waste products was employed when hyperpotassaemia, loss of sodium, or dehydration did not respond to the above-mentioned measures. In such cases peritoneal lavage (rather than the artificial kidney) was resorted to for 6 to 12 hours at a time, and repeated if necessary. In all, 76 patients were treated in this way on 84 occasions [but the recovery rate in these cases is not mentioned]. *L. H. Worth*

159. **Prolonged Anuria. Successful Management by Continuous Infusion into the Inferior Vena Cava**
C. S. RUSSELL, C. J. DEWHURST, and J. C. BRACE. *Lancet* [*Lancet*] **1**, 902–905, May 1, 1954. 1 fig., 11 refs.

160. **The Mechanism of Proteinuria.** (Zum Mechanismus der Proteinurie)
K. JAHNKE and W. SCHOLTAN. *Deutsches Archiv für klinische Medizin* [*Dtsch. Arch. klin. Med.*] **200**, 821–836, 1953. 5 figs., 25 refs.

In 20 cases of chronic nephritis a careful analysis confirmed the observation that what is commonly called "albuminuria" is in fact a proteinuria, the deposit obtained on heating containing both albumin and globulin, the fractions of which could be separated and identified by means of electrophoresis and the ultracentrifuge. The same albumin and globulin fractions were present in the urine as in the serum, with the exception of 2 (out of 3) cases of myelomatosis in which the urine contained no albumin, β and γ globulins only being present. Usually the albumin content of the urine exceeds that of globulin, and in the presence of a normal serum protein level constitutes up to 75% of the total protein excreted in the urine. In cases of hypoproteinaemia, however, as in lipoid nephrosis, the ratio may be reversed.

By ultracentrifugation at 50,000 r.p.m. (180,000 *g*) it was shown that the largest globulin molecules commonly found in the serum (Fraction M, with a molecular weight of about 1,000,000) were not present in the urine, while those of the next largest size (Fraction G, molecular weight about 300,000) were present in only half the cases. The bulk of the urinary globulin fraction belonged to Fraction A, with a molecular weight of 70,000 or less, or to the even smaller Fraction X, their concentration in the urine in many of the cases exceeding that in the serum.

The authors suggest that in diseases in which the mechanism of glomerular filtration is affected the presence in the urine of globulins of low molecular weight in greater proportions than are usually found in the serum may be due to proteolysis of the larger serum globulins while passing through the nephron, whereas in infectious and inflammatory conditions affecting the calices and lower urinary tract globulin molecules similar or equal in size to those in the serum may be present in the urine as a result of serous exudation, while tubular diffusion into the urine of globulin molecules of large size (Fraction G) may occur in nephrosis.

Only a small proportion of the globulin present in the urine in chronic nephritis belongs to the γ and β groups. It is thought that these globulins circulate in the blood stream as part of lipid compounds forming molecules of great magnitude which are incapable of passing even through the diseased glomerular filter or any other part of the nephron, and that when these compounds undergo separation the lipid fraction is held back by the renal tissues and the γ and β globulins are split into smaller fractions. *L. H. Worth*

161. **Hyperpotassaemia in Nephritis.** (L'hyperkaliémie au cours des néphrites)
P. VALLERY-RADOT, C. LAROCHE, J. HAZARD, J. PAOLAGGI, and J. TRUFFERT. *Presse médicale* [*Presse méd.*] **61**, 1706–1708, Dec. 25, 1953. Bibliography.

The authors discuss, with many references to the literature, the problem of retention of potassium in renal insufficiency. In 10 out of 13 of their patients with acute nephritis in the initial stage of anuria the serum potassium level did not rise until the end of the first week, but after the onset of diuresis it fell more quickly than did the concentration of non-protein nitrogen constituents. In patients with chronic nephritis the degree of potassaemia was linked with the onset of renal failure; in these cases, increased diuresis was not accompanied by an early and quick shedding of the excess serum potassium.

The general somatic effects due to hyperpotassaemia included asthenia, cramps, flaccid paralyses, disturbances of the respiratory rhythm, cardiovascular accidents, and abnormalities in the electrocardiogram. Some therapeutic measures and their results are discussed. Restriction of fruit juices and vegetables, in view of their high potassium content, is desirable, and a low-protein diet rich in carbohydrates and fats is recommended, together with glucose transfusions (10 to 20% solution to which one unit of insulin for every 2 g. of glucose should be added) as a potential check on damage to liver and muscle tissue due to possible hyperpotassaemia. The administration of calcium has no direct effect on the hyperpotassaemia, but may attenuate its toxic action generally. Other therapeutic measures such as exchange transfusion and the administration of digitalis and cation-exchange resins have been tried in these cases, but have given only equivocal results.

L. H. Worth

162. **Chronic Interstitial Nephritis.** (Die chronisch-interstitielle Nephritis)
O. SPÜHLER and H. U. ZOLLINGER. *Zeitschrift für klinische Medizin* [*Z. klin. Med.*] **151**, 1–50, 1953. 18 figs., bibliography.

The authors here record brief case histories, with clinical and pathological observations, of 44 patients treated at the University Medical Polyclinic, Zürich, since 1940 for a chronic form of renal deficiency which in many respects did not seem to fit into the common pattern of chronic nephritis. In most cases the onset was asymptomatic and insidious, and in the early stages most of the patients complained of nothing more than lassitude, which was diagnostically misleading. Anaemia was an early sign, accompanied by a minimal albuminuria and scanty urinary deposit of blood cells. Blood pressure, kidney function, blood electrolyte balances, and alkali reserve were normal.

After this first phase, which rather resembled a focal nephritis, the disease progressed to sclerosis of the interstitial stroma and began to affect the adjoining structures, mainly Henle's loops of the tubules. Early signs of renal dysfunction were hyposthenuria, reduced urea clearance, delayed excretion of phenol red, and increased excretion of potassium, calcium, and chloride. The later stages of the disease were marked by hypertension, isosthenuria, a urea clearance of less than 30% of normal values, and reduced excretion of electrolytes. In this stage deterioration was rapid and could no longer be influenced by any therapeutic measures, although in a few cases strict dietary procedures, large doses of vitamins, or decapsulation succeeded in prolonging life.

Thirty of the patients died. At necropsy the kidneys were found to be small in 18 cases, but scarring of the surface was usually absent. The main histological features were the inflammatory infiltration and increase of the stroma with absence of granulation tissue. Crescents, tubular adhesions, and other signs of a past glomerulitis were all absent, but there was gross hypertrophy of the connective tissue immediately surrounding the hyalinized glomeruli. In 22 cases papillary necrosis, of recent origin in some cases, was present. In all cases only the larger arteries were abnormal; these showed a circular thickening of the intima with elastosis; in only one case was arteriolar necrosis, which is usually present in malignant nephrosclerosis, observed.

The authors are unable to offer any explanation of the cause of this clinical and pathological entity, but suggest that the widespread use of sulphonamides and antibiotics and the appearance of this formerly unknown syndrome of renal dysfunction may not be merely coincidental. In their view, it is not impossible that although sulphonamides and antibiotics may clear up an infection in the urinary pathways, they may also cause a slowly progressive structural change in the renal stroma.

L. H. Worth

163. **Aureomycin Therapy of Chronic Prostatitis**
W. E. SCHATTEN and L. PERSKY. *Surgery, Gynecology and Obstetrics* [*Surg. Gynec. Obstet.*] **98**, 40–44, Jan., 1954. 4 refs.

The authors report their experiences at the University Hospitals, Cleveland, Ohio, with aureomycin in the treatment of 20 patients suffering from prostatitis unassociated with any other genito-urinary disease. The drug was given by mouth as follows: 10 patients received 250 mg. twice a day for one month; 5 received 500 mg. twice a day for 3 weeks; and 5 received 1 g. twice a day for 3 weeks. Prostatic massage was carried out weekly in all cases.

Permanent sterilization of the urine was achieved in only one patient, who had received 250 mg. twice a day for one month. Of the various types of organism isolated from cultures of urine and prostatic secretion before treatment, 37% were eradicated by aureomycin. However, many other organisms appeared during and after treatment. These bacteriological findings did not appear to be influenced by the prostatic massage. Although there was symptomatic improvement in all cases within 4 to 5 days, signs and symptoms returned in 19. The urine in all cases contained an adequate concentration of aureomycin, but the prostatic secretion contained only small amounts. The lack of success in so large a percentage of cases is attributed to this latter finding.

Thomas Moore

Endocrinology

THYROID GLAND

164. **A Form of True Hyperthyroidism (Basedow's [Graves's] Disease without Exophthalmos) due to the Consumption of Iodized Bread.** (Een vorm van genuine hyperthyreose (M. Basedow zonder exophthalmus) na gebruik van gejodeerd brood)
E. VAN LEEUWEN. *Nederlandsch tijdschrift voor geneeskunde* [*Ned. T. Geneesk.*] **98**, 81–89, Jan. 9, 1954. 2 figs., 2 refs.

In August, 1948, the use of iodized salt in the baking of bread became compulsory in the Netherlands towns of Emmen and Odoorn as a prophylactic measure against endemic goitre—the water-supply in this area having a low iodine content—and the consumption of iodine per person was probably increased by 120 to 160 μg. daily. Since then a number of cases of hyperthyroidism have been observed which, while manifesting the nervousness, tachycardia, warmth, moist skin, tremor, emaciation, and increased metabolism of Graves's disease, have differed therefrom in their higher age incidence, less frequent enlargement of the thyroid gland, and, most noticeably, absence of exophthalmos. Whereas during the period 1938–49 the author saw only 9 cases of hyperthyroidism from this area, he saw 62 cases between 1949 and 1953, 58 of which were without exophthalmos. The occurrence of this apparent increase in incidence of hyperthyroidism in Emmen and Odoorn associated with an increased consumption of iodine is attributed to the presence of a number of latent cases which became manifest when an iodine-rich diet was substituted for the previous iodine-poor one, although the results of withdrawal of the iodine source in a few cases were inconclusive.

It is also suggested that the condition seen here represents a form of primary hyperthyroidism which is found in association with an iodine-rich dietary, and which differs in aetiology from the classic form with exophthalmos, which is thought to be independent of the iodine content of the soil. The possible effects of iodine excess should be considered in determining prophylactic measures against endemic goitre. *R. Crawford*

165. **Granulomatous or Giant Cell Thyroiditis. A Clinical and Pathologic Study of Thirty-seven Patients**
S. LINDSAY and M. E. DAILEY. *Surgery, Gynecology and Obstetrics* [*Surg. Gynec. Obstet.*] **98**, 197–212, Feb., 1954. 22 figs., 26 refs.

The aetiology, pathogenesis, and treatment of granulomatous or giant-cell thyroiditis are discussed, with reference to 37 cases. As regards the incidence of this form of thyroid disease, the authors state that at the University of California Hospital, Los Angeles, between 1920 and 1952 thyroidectomy was performed on 7,263 patients, 23 (0·3%) of whom had granulomatous or giant-cell thyroiditis, 220 had proved Hashimoto disease, and 2 had Riedel's thyroiditis. The disease is moderately acute in onset, with fever and malaise, and usually lasts a few days to a few months. It affects females more frequently than males, and the majority of the patients are in the fourth or fifth decades. Dysphagia and tenderness of the thyroid gland precede hoarseness and a choking sensation, the gland gradually becoming firmer.

Of 25 patients treated by thyroidectomy, 13 subsequently became hypothyroid; the remaining 12 were not followed up. Of the 12 who were not operated on, 3 required permanent thyroid medication for hypothyroidism after the acute stage of the illness.

Discussing laboratory investigations in the diagnosis of granulomatous thyroiditis the authors state that in most cases the basal metabolic rate is normal but the erythrocyte sedimentation rate is raised. A most striking finding, and one which is of value in diagnosis, is that of an increase in the serum protein-bound iodine level in the acute phase although the uptake of ^{131}I is depressed; in no other disease of the thyroid does this paradox exist. Microscopical examination of the gland reveals focal follicular degeneration associated with inflammation, followed by proliferation of the residual follicular wall. Reorganization of small follicles originates in part from multinucleated giant cells. Extensive fibrosis is also seen in some cases.

No improvement was obtained in the authors' cases from treatment with thiouracil or antibiotics. It is suggested that administration of cortisone or *x* irradiation to an average total dose of 800 r, is the treatment of choice at the present time. *Guy Blackburn*

ADRENAL GLANDS

166. **On the Mechanism of Melanin Pigmentation in Endocrine Disorders**
A. B. LERNER, K. SHIZUME, and T. B. FITZPATRICK. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **21**, 337–338, Dec., 1953. 4 refs.

The authors present from the University of Oregon Medical School, Portland, Oregon, a preliminary report on the results of injection into 3 human subjects of an extract of hog pituitary glands containing an appreciable amount of the melanocyte-stimulating hormone (M.S.H.), one of the samples tested having a potency of 100,000 units of M.S.H. per mg. The subjects, a 41-year-old white man, a 55-year-old white man with vitiligo of long duration, and a 29-year-old negress, also with long-standing vitiligo, were given intramuscular injections of 4·18 g., 3·12 g., and 4·5 g. of M.S.H. over periods of 36, 32, and 50 days respectively. In all 3 patients there was a general increase in normal pigmentation, which returned to its previous state in from 2½ to 4 months

after administration of M.S.H. was discontinued. Of the 2 cases of vitiligo, no effect was produced in the vitiliginous areas in the white man, but in the negress there was a small degree of perifollicular pigmentation.

Since the urinary excretion of M.S.H. is increased during pregnancy and in Addison's disease, and since injection of M.S.H. has been shown to produce increased pigmentation in normal man, the authors suggest that excess production of the melanocyte-stimulating hormone by the pituitary gland may be in large part responsible for the pigmentation in these conditions. (A fully detailed report is promised at an early date.)

D. G. Adamson

167. **Effect of *para*-Aminobenzoic Acid on the Metabolism of Cortisone in Liver Tissue**

L. L. WIESEL. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 80–82, Jan., 1954. 8 refs.

Studies of the metabolism of cortisone in slices of rat and human liver have confirmed the author's previously published conclusion [see Abstract 188] that *para*-aminobenzoic acid interferes with the inactivation of cortisone by liver tissue. It interferes markedly with the rapid reduction of the unsaturated conjugated system of the cortisone molecule, while permitting more rapid degradation of the side-chain. *W. S. C. Copeman*

168. **The Effect of Cortisone on the Survival of Guinea Pigs Inoculated with Diphtheria Toxin**

C. B. FAVOUR, L. T. ATLAS, M. I. LEVINE, and C. K. OSGOOD. *Laboratory Investigation* [*Lab. Invest.*] **3**, 1–18, Jan.–Feb., 1954. 4 figs., 23 refs.

At the Peter Bent Brigham Hospital (Harvard Medical School), Boston, three experiments were performed with groups of 102, 200, and 52 guinea-pigs respectively in a study of the effect of cortisone on survival after inoculation of diphtheria toxin, 5 mg. of cortisone being injected twice daily intramuscularly before, during, and after inoculation with varying doses of the toxin. More of the cortisone-treated animals than of controls survived during the first 4 or 5 days, but thereafter they died at a greater rate and at the end of 10 days after inoculation the over-all mortality was the same in the two groups. It was noted that the effect of cortisone on survival time was greatest in the animals receiving 0·5 to 1·6 MLD of toxin, and was less marked with larger or smaller doses of the toxin.

In discussing these results, the authors suggest that cortisone may delay the absorption of toxin into the body fluids. *B. Nordin*

169. **Cortisone in the Treatment of Chronic Adrenal Insufficiency**

P. FOURMAN and A. R. HORLER. *Lancet* [*Lancet*] **1**, 334–336, Feb. 13, 1954. 32 refs.

The results achieved with cortisone in the treatment and maintenance of 8 patients with Addison's disease and 3 with hypopituitarism, who were followed up at the Radcliffe Infirmary, Oxford, over a period of 18 months, are briefly summarized. Most of the patients with Addison's disease had received deoxycortone acetate and salt previously, and the addition of cortisone usually resulted in the dosage of the former being halved. For maintenance, 10 to 25 mg. of cortisone was given daily in four divided doses, but much larger amounts were required during crises. In most cases appetite improved and the patient experienced a sense of well-being and an increase in initiative and vigour. In 6 of the patients with Addison's disease there were healed or active tuberculous lesions but cortisone did not appear to affect this condition. *A. C. Crooke*

170. **The Adrenal Response to Corticotrophin. Effect of A.C.T.H. on Plasma Adrenal Steroid Levels**

R. I. S. BAYLISS and A. W. STEINBECK. *British Medical Journal* [*Brit. med. J.*] **1**, 486–490, Feb. 27, 1954. 3 figs., 13 refs.

The authors, working at the Postgraduate Medical School of London, have assessed the response of the adrenal glands to stimulation by ACTH (corticotrophin) given by various routes by measuring the changes produced in the plasma content of 17:21-dihydroxy-20-ketosteroids (such as hydrocortisone, cortisone, and their metabolic reduction products). The method of assay used by the authors has been described elsewhere (*Biochem. J.*, 1953, **54**, 523).

The drug was administered by intravenous infusion to 12 subjects, only 2 of whom " were not clinically ill at the time of study ", the remainder suffering from a variety of diseases. An increase in the plasma steroid level appeared within 15 to 30 minutes of starting the infusion, the level reaching its maximum in most cases after one hour, remaining fairly constant during the infusion, and falling rapidly after its completion. A maximal response was obtained in most cases with a dose of one unit of ACTH per hour for 6 to 8 hours, the plasma steroid level rising to between 24 and 36 μg. per 100 ml. After repeated daily infusions in 2 cases a higher level was obtained, suggesting that repeated stimulation of the adrenal cortex increases its hormone output. A single intramuscular injection of 80 units of ACTH in gelatin (" acthar " gel) was given to 17 patients, " all of whom were comfortable at the time of study, except three with asthma ". The plasma steroid level began to rise within 2 hours and reached its maximum between 4 and 8 hours after the injection, falling to normal in most cases within 12 to 24 hours. Injections of 20 units of ACTH as acthar gel produced a more transient elevation of the plasma steroid level, although in some cases the maximum level reached did not differ significantly from that obtained with 80 units. In 5 cases in which repeated injections of acthar gel were given there was again a progressive increase in response.

A single intramuscular injection of ACTH dissolved in saline was given to 16 patients, 8 of whom were "clinically ill ", the maximum response being obtained after 1 to 2 hours and the effect of the injection passing off within 4 to 6 hours. The degree of response was very variable, however, and in 2 cases was negligible.

It is concluded that intravenous infusion is probably the most reliable, and certainly the most economical, method of administration of ACTH.

Nigel Compston

171. **The Relation between the Number of Eosinophils in Blood and Bone Marrow under Ordinary Conditions and under the Influence of ACTH.** [In English]
H. UHRBRAND. *Acta haematologica* [*Acta haemat. (Basel)*] **11**, 11–20, Jan., 1954. 2 figs., 25 refs.

The investigation here reported was undertaken at the Frederiksberg Hospital, Copenhagen, to determine whether the number of eosinophil cells present in the bone marrow changes when the eosinophil count in the blood decreases under the influence of ACTH (corticotrophin). At the same time a study was made of the relation between the eosinophils of the blood and bone marrow under normal conditions, about which there has been considerable difference of opinion. For the latter purpose specimens of blood and bone marrow from 31 patients were examined; 8 of these were suffering from allergic disorders (6 from asthma and 2 from drug eruptions), while the remainder had various diseases, none of which was likely to affect the eosinophil count. It was found that a low count in the blood (expressed as percentage of the total leucocyte count) corresponded to a low count in the marrow (expressed as percentage of all nucleated cells), and that when the count was increased in the blood there was also a higher count in the marrow. In the 5 patients whose blood showed the highest eosinophil counts the percentage was lower in the marrow, whereas in the remainder the marrow count was consistently slightly higher. The effect of ACTH was then observed on 13 of the same patients, including the 6 asthmatics, blood and bone-marrow specimens being examined 4 to 6 hours after a single dose of 20 to 40 mg. of ACTH, in 9 cases also after 3 days' treatment with 20 mg. 3 times daily, and in one case also before and after a dose of cortisone. The eosinophil values were expressed as in the previous series as a percentage of the total leucocyte or nucleated-cell count. It was found that 4 to 6 hours after the dose of ACTH the eosinophil count in the blood was decreasing, while that in the marrow was rising. The initial rise did not persist, however, and after 3 days' treatment the eosinophil count in the marrow was in no case greater than it had been before the ACTH had been given.

V. C. Medvei

172. **The Role of the Reticulo-endothelial System in the Eosinopenic Reaction to Glucocorticosteroids.** (Die Rolle des retikulo-endothelialen Systems für die eosinopenische Reaktion unter Gluco-Corticosteroiden)
A. F. ESSELLIER, H. R. MARTI, and L. MORANDI. *Acta haematologica* [*Acta haemat. (Basel)*] **11**, 21–30, Jan., 1954. 5 figs., 29 refs.

The effect of blocking the reticulo-endothelial system of the guinea-pig on the peripheral eosinopenia normally produced by the injection of ACTH (corticotrophin) was investigated in experiments carried out at the Medical Clinic of the University of Zürich. Blocking was achieved by the subcutaneous injection of a 1% aqueous solution of trypan blue, which is stored in the reticulo-endothelial system, 2 ml. being given on the first day and then 1 ml. every other day up to a total of 18 ml. Male guinea-pigs of 500 to 700 g. were used, some with a normal eosinophil count (up to 360 per c.mm.), some with a constant increase (up to 6,600 per c.mm.). ACTH (10 units) or cortisone (0·625 mg. per 100 g. body weight) was given 24 hours after the last injection of trypan blue, and changes in the eosinophil count compared with those in a significant number of control animals which had not received trypan blue. The experiments were planned and evaluated statistically.

It was found that the eosinopenic effect of ACTH and of cortisone was diminished considerably by blockade of the reticulo-endothelial system, or even suppressed entirely. When the dose of cortisone was increased to 2·5 mg. per 100 g., however, a significant fall in the eosinophil count was achieved even in animals treated with trypan blue.

This effect, being obtained with cortisone as well as ACTH, must be independent of the adrenal cortex. It is thus concluded that the reticulo-endothelial system plays an important part in the mechanism of the eosinopenia caused by glucocorticosteroids.

V. C. Medvei

DIABETES MELLITUS

173. **Infants of Diabetic Mothers with Special Reference to Neonatal Adrenocortical Function as Assessed by Urinary Excretion of Corticoids and Tests using Adrenocorticotrophic Hormones.** [In English]
S. I. BJÖRKLUND. *Acta endocrinologica* [*Acta endocr. (Kbh.)*] **15**, 25–32, Jan., 1954. 19 refs.

The author, working at the Flensburg Children's Hospital, Malmö, Sweden, has investigated the adrenocortical activity of newborn infants of diabetic mothers with some interesting results.

In all, 7 such infants were studied between the first and 14th days of life, and 3 infants of non-diabetic mothers acted as controls. Where possible, 24-hour specimens of urine were used for corticoid estimation, and up to 6 such estimations were performed in each case. The eosinopenic response to 5 mg. of ACTH was also assessed in 5 of the cases, eosinophil counts being made before and 6 hours after administration of corticotrophin. The urinary corticoids present were thought to represent 11-oxycorticosteroids and 11-deoxycorticosteroids, together with other as yet unrecognized corticoids.

The results, which were expressed in mg. per sq. metre of body surface and in μg. per kg. body weight, showed that there was a significant increase in urinary corticoid excretion in 6 of the 7 infants as compared with the control subjects and with the values for normal infants published by other workers. Four of the 5 infants were thought to show a significant eosinopenia following administration of ACTH. It was also shown that the urinary excretion of corticoids fell progressively from the initial high figure.

The author offers the intriguing suggestion that this increase in corticoid secretion offsets the hyperinsulinism supposedly present in infants of diabetic mothers, as judged by the finding of pancreatic islet-cell hyperplasia. He also assumes that the high birth weight.

Cushing-like appearance, and oedema, all of which were lost rapidly in the first week, are due to the over-production of corticoids, which, however, tends to correct itself within the first week of life. He claims to have shown by electrocardiography that there is also evidence of hypokalaemia in such infants, and suggests that the administration of potassium salts might usefully be added to the usual treatment of these cases.

[This would appear to be an important paper, and further observations with larger numbers would be valuable. Figures for the eosinophil counts following administration of ACTH are rather equivocal in all except 2 of the cases.] *J. N. Harris-Jones*

174. **Blood Sugar in Newborn Infants of Diabetic Mothers.** [In English]
J. PEDERSEN, B. BOJSEN-MØLLER, and H. POULSEN. *Acta endocrinologica* [*Acta endocr.* (*Kbh.*)] **15**, 33–52, Jan., 1954. 7 figs., 17 refs.

The authors, in this detailed study of the blood sugar levels in 27 newborn infants of diabetic mothers carried out at the Rigshospitalet, Copenhagen, investigated three phenomena: the variations in the blood sugar level over the first 24 hours of life, variations in the level over the first 9 days of life, and the relationship between the well-known complications which occur in these infants and the blood sugar values. Similar studies were made in 28 infants of non-diabetic mothers as a control. The diabetic mothers were divided into either " long-term " or " short-term " subjects, depending on whether they had been under treatment before or only after the 53rd day before delivery, and whether the period in hospital before delivery had exceeded or was less than 32 days. The blood sugar level of the diabetic mothers was estimated for varying periods before delivery (" pregnancy level "), and at the moment of delivery (" delivery level "). Care was taken to obtain blood from the infants during a fasting state, and all estimations were performed in duplicate.

Blood sugar levels, estimated at birth in cord blood and later in capillary blood at 2-hourly intervals over the first 24 hours, showed that whereas the cord blood sugar level was higher in the " diabetic " group than in the controls, there was no significant difference between these two groups over the subsequent 24 hours.

In the 9-day study, the average fasting blood sugar level of 16 infants of diabetic mothers was not significantly different from that of 11 infants of non-diabetic mothers studied over the same period. More detailed analysis, however, showed that when the maternal blood sugar level had been kept within normal range for at least 52 days before delivery (long-term subjects) neither the 24-hour blood sugar curve nor the 9-day blood sugar curve differed from normal; this did not hold for the infants of diabetic mothers not so well controlled (short-term subjects), in whom the blood sugar level tended to fall to abnormally low values. This is in agreement with the observation that the blood sugar level of infants of both diabetic and non-diabetic mothers is, at the moment of birth, positively correlated with the maternal level; but during the first 24 hours of life, and to a lesser extent over the first 5 days, the levels of the infant's and mother's blood sugar are inversely related, in that the blood sugar level is least depressed in those infants whose mothers' blood sugar level has been under control for a period before delivery.

Lastly, there was no significant difference between the blood sugar levels in blood taken during attacks of cyanosis and respiratory arrest occurring in infants of diabetics and in that taken during the absence of such symptoms. This observation, the authors suggest, would seem to cast doubts on the common practice of administering glucose to infants of diabetic mothers. Indeed, in their view, such a proceeding may be indirectly harmful, and they conclude that major neonatal hypoglycaemia can best be avoided by maintaining the maternal blood sugar at a low level during pregnancy and at a high level during delivery.

J. N. Harris-Jones

175. **The Growth of Juvenile Diabetics.** [In English]
N. BERGQVIST. *Acta endocrinologica* [*Acta endocr.* (*Kbh.*)] **15**, 133–165, Feb., 1954. 8 figs., bibliography.

At the General Hospital and Flensburg Children's Hospital, Malmö, Sweden, growth disturbances were observed in 56 children in whom diabetes was diagnosed before the age of 15 years. In 3 cases growth was recorded for some years before the onset of diabetes and in 21 from the time of onset. The majority of the patients ate the same food as their families, except that sugar was forbidden; any further limitation of intake of carbohydrate was the exception. All the patients received insulin from the onset, the aim being to keep them symptom-free and to avoid both hypoglycaemia and acidosis. Height curves for different age groups were compared with those for healthy Swedish children in similar age groups.

The cases were divided into three groups according to age at onset of the diabetes. In the first group, 0 to 5 years, there were 11 boys and 10 girls, and height measurements were started on the average 4·5 and 5·3 years respectively after onset. At that time the boys were slightly below normal and the girls significantly so. The second group, with onset at 5 to 10 years, included 10 boys and 7 girls, all of whom were retarded in growth during the period of observation. In the third group, with onset at 10 to 15 years, 8 boys showed marked retardation while 10 girls showed no deviation from the normal. The mean retardation in the 29 boys during an average observation period of 5·1 years was 4·1 cm. and in 27 girls observed for 5·6 years it was 1·0 cm.

To determine the cause of the retardation, the characteristic features of 11 diabetic dwarfs were studied, a diabetic dwarf being defined as a subject whose height during or after growth was below the lower limit of the normal variation found in the height standards of Broman *et al.* (*Acta paediat.* (*Stockh.*), 1942, **30**, 1). The disease began in all cases before the age of 9½ years (average 5·4 years). Hepatomegaly, hypogonadism, and retarded sexual development were noted in 9 cases for which reliable information was available. 17-Ketosteroid excretion was low in all 11 cases, both males and females.

Skeletal development, as judged from radiographs of the epiphyses of the hands and wrists, was retarded in only 3 of 9 cases in which this was studied. To determine the extent to which the low stature of diabetic dwarfs was constitutional, the author collected information concerning the relatives; this revealed that in 8 of the 11 families the relatives were of low stature. The author suggests, however, that this is not the only factor causing retarded growth, and that the lack of insulin is " at least a major cause ". The more marked retardation in boys may be explained by defective gonadal function. He suggests that while androgens are important for growth in boys, oestrogens do not have the same effect on girls.

J. Lister

176. **The Influence of Pregnancy on Diabetes.** [In English]

N. BERGQVIST. *Acta endocrinologica* [*Acta endocr. (Kbh.)*] **15**, 166–181, Feb., 1954. 1 fig., bibliography.

The influence of pregnancy on the diabetic state was studied in 42 diabetic women living in Malmö (total number of pregnancies 54). Treatment of the diabetes was directed towards keeping the patient symptom-free and avoiding polyuria and ketosis, the degree of severity of the disease being judged by the total insulin dose. Estimation of the average dose at the end of each month of pregnancy showed that up to the fourth month there was a slight decrease, after which the dose increased, chiefly during the seventh month. Of the 54 pregnancies, 27 continued beyond the 36th week. Between them and parturition one of the 27 patients required insulin for the first time; of the remainder, all of whom had been receiving insulin, the dose was increased in 2, decreased in 6, and unchanged in 14; 4 received no insulin after the 36th week. Severe hypoglycaemia occurred in 4 cases between the 13th and 18th weeks and in one case immediately before delivery. In 30 of 35 cases in which the puerperal diabetic state could be assessed a marked improvement was observed in carbohydrate tolerance, as manifested by a decrease in insulin dosage, hypoglycaemia, reduced glycosuria, and reduced ketosis.

Diabetes was diagnosed for the first time in 11 of the 42 cases—in 3 of them during routine examination of the urine, while in 8 there were severe diabetic symptoms. Ketonuria was noted in the first trimester in only one case and in the second trimester in 4 cases, but diabetic ketosis was found in 28 cases in the third trimester.

The author believes that in pregnancy there is a diabetogenic mechanism which is capable of " exacerbating an existing diabetes or of manifesting a subclinical diabetes ". This mechanism predominates only during the latter half of pregnancy and disappears with parturition, probably leaving no lasting results. Discussing the nature of the mechanism, he suggests that the increased production of adrenocorticotrophic hormone which is known to occur during pregnancy comes, at least in part, from the placenta. It is noteworthy that the increase in the urinary excretion of corticoids is maximal at the seventh month, when the decrease in carbohydrate tolerance is most marked. The rapid improvement in the diabetic state during the puerperium suggests that the removal of the placenta, with the abrupt cessation of secretion of diabetogenic hormones, is responsible. *J. Lister*

177. **Hypertrophy and Hyperplasia of the Pancreatic Islets in New-born Infants**

B. S. CARDELL. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **66**, 335–346, Oct., 1953 [Received Jan., 1954]. 2 figs., 37 refs.

An investigation was undertaken at King's College Hospital, London, to determine the normal range in the amount of pancreatic islet tissue present in the newborn infant and the amount present in infants of diabetic mothers. Blocks of tissue were removed from the pancreas of 18 infants of diabetic mothers, 38 infants of non-diabetic mothers, and 3 infants with erythroblastosis foetalis. After the tissue had been fixed in formalin, stained sections from paraffin blocks were examined microscopically and the amount of islet tissue in the gland estimated. The author's findings confirm those of other workers—namely, that the amount of islet tissue in the pancreas of the newborn infant varies within a wide range (0·7 to 2·6% of the total pancreatic tissue), but that a true increase is common in infants of diabetic mothers (1·8 to 9·9% of the total pancreatic tissue). The increase in the latter group is apparently due to hypertrophy and hyperplasia of β cells, possibly through over-production by the maternal pituitary gland of the diabetogenic growth hormone. A close relationship was found between the amount of islet tissue present and the body weight of the infant. In the infants with erythroblastosis foetalis the amount of islet tissue was within the normal range. *A. Wynn Williams*

178. **Serum Glucuronic Acid Levels in Diabetes Mellitus**

A. SALTZMAN, W. T. CARAWAY, and I. A. BECK. *Metabolism* [*Metabolism*] **3**, 11–15, Jan., 1954. 2 figs., 17 refs.

Having observed an increase in the serum glucuronic acid level in some cases of diabetes, the authors carried out a controlled investigation at the Rhode Island Hospital, Providence, to determine the relationship, if any, between this finding and the blood glucose level, insulin requirements, and the severity of the diabetes in a mixed group of 134 diabetics and a group of 27 diabetics who received no drugs and no insulin on the morning of the test; 37 healthy subjects served as controls. A group of 21 patients with various hepatic lesions were also examined. The blood glucose level was estimated by Benedict's method, and the serum glucuronic acid content by the method of Fishman. It was found that the normal range for the glucuronic acid level was 1·6 to 3·6 mg. per 100 ml., somewhat lower than that reported by other workers, probably because the authors' readings were corrected for the blood glucose content and serum was used in preference to whole blood.

The results showed that there was a significant rise in the serum glucuronic acid level in 56·6% of diabetics as a whole, but that the increase was not significant in controlled cases. There was no relationship between this increase and insulin requirements. A very high con-

centration was found in 2 cases of the Kimmelstiel–Wilson syndrome and a significant increase was noted in the patients with liver disease.

The authors conclude that since glucuronic acid is produced from liver glycogen, there is an increase in conversion of glycogen to glucuronic acid in liver disease and diabetes; this confirms the finding of glycogen depletion of the liver in both diseases. They suggest, however, that as a result of faulty carbohydrate metabolism in diabetes, there is an increased demand on glucuronide conjugation to remove excess endogenous metabolites.

[Readers are advised to consult the original article for details of the chemical and statistical methods employed.]

J. N. Harris-Jones

179. **Fructose Tolerance in Diabetes Mellitus.** (Über die Verträglichkeit der Fructose bei Diabetes mellitus)
P. PLANCHEREL and S. MOESCHLIN. *Schweizerische medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **84**, 28–31, Jan. 9, 1954. 2 figs., bibliography.

At the University Medical Clinic, Zürich, 32 patients with well-controlled diabetes (3 of them treated with diet only) were given varying quantities of fructose in addition to their normal diet. The daily supplements ranged from 16 to 160 g. and the period of observation from 4 to 50 days. It was found that little or no fructose could be detected in morning fasting blood samples, and that the highest blood fructose level recorded during the day was 35 mg. per 100 ml. Less than 2% of the fructose ingested was excreted in the urine. In 6 cases there appeared to be a rise in the total blood sugar level (but 3 of these patients had infections of one kind or another) and in 6 there was increased glycosuria. In 2 patients it was found necessary to raise the insulin dosage to maintain good control, but in 7 others it was possible to reduce it during the experimental period. There did not appear to be any decline in fructose tolerance, even in the patients given the largest doses for the longest time.

B. Nordin

180. **Transfer to Insulin Zinc Suspension**
M. G. FITZGERALD, P. A. THORN, and J. M. MALINS. *Lancet* [*Lancet*] **1**, 187–190, Jan. 23, 1954. 3 figs., 5 refs.

At the General Hospital, Birmingham, the authors observed the effect of changing the existing insulin regimen of diabetic patients to an equivalent dose of insulin zinc suspension (I.Z.S.). In all, 30 patients were studied, the 24 out-patients among them being admitted to hospital for two 36-hour periods, during which time 2-hourly blood sugar estimations were performed over 24 hours, and the urinary sugar content estimated in two 12-hour samples. During their short stay in hospital "home conditions" were followed as closely as possible. Upon discharge after these investigations had been completed existing insulin therapy was replaced by an equal dose of I.Z.S., and 6 days later the patient was readmitted for another 36 hours for further biochemical study. The mean level of the 2-hourly blood sugar estimations and also the maximum variation in blood sugar level before and after transfer to I.Z.S. were then compared. Diabetic control was considered to have improved if both the mean blood sugar level and the maximum variation were decreased after transfer. Diabetic status was considered to have been made worse if diabetic symptoms appeared where none existed before transfer, or if the mean blood sugar level increased by at least 50 mg. per 100 ml. after changing to I.Z.S.

The authors found that control of the diabetes was unaltered in 17 cases, worse in 10 cases, and better in only 3. Worsening of the diabetic state was particularly noticeable where the patients had previously been taking soluble insulin or insulin mixtures containing a high ratio of soluble to protamine zinc insulin.

These results are at variance with those reported by other workers. The authors point out that most of their cases were in poor clinical and biochemical control before transfer, and this, and perhaps also the type of insulin being used before transfer, may in part account for their somewhat unexpected results. In 2 cases, change to an equivalent dose of I.Z.S. was followed by an acute diabetic state, requiring an increased insulin dosage. It is suggested that in cases in strict biochemical control, the distribution of dietary carbohydrate may have to be altered at the time of transfer. In their opinion, transfer to insulin zinc suspension from other types of insulin is not without risk.

J. N. Harris-Jones

181. **Diabetic Neuropathy. A Clinical Study of 150 Cases**
M. M. MARTIN. *Brain* [*Brain*] **76**, 594–624, 1953. Bibliography.

The author has investigated, at King's College Hospital, London, the neurological abnormalities in a series of 150 diabetic patients, in 40 of whom neurological symptoms were the presenting feature. The most common symptom was pain, sometimes severe: the most common sign, abnormalities in the tendon reflexes, the ankle-jerk being absent in four-fifths of the cases, and one or both knee-jerks in one-third. Sensory loss was also commonly observed, light touch and pain sensation being impaired or lost in 75% of the patients.

Evidence of involvement of the peripheral autonomic system was found in all of 20 unselected cases, as evidenced by alteration in reflex vasoconstriction, vasodilatation, or sweating. Impotence was present in 38 (54%) of the 70 male patients, and nocturnal diarrhoea and neuropathic bladder dysfunction were also considered to be evidence of disturbance of the autonomic nervous system. Neuropathic bone and joint lesions were present in 6% of the series, being almost always confined to the peripheral joints; 2 cases of general osteoporosis of the feet are described, of which the only apparent cause was the diabetic neuropathy.

The author concludes that diabetic neuropathy occurs most frequently in diabetics in whom the disease is poorly controlled or has remained unrecognized for a long period of time. It is considered that the development of the neuropathy is related, not to concomitant vascular disease or vitamin-B deficiency, but to the fundamental metabolic disorder of diabetes mellitus.

Fergus R. Ferguson

The Rheumatic Diseases

182. **Clinical and Experimental Studies of the Mode of Action of Heparin in Rheumatic Fever.** (Ricerche clinico-sperimentali sul meccanismo d'azione dell'eparina nella malattia reumatica)
F. DE MATTEIS and F. PANIGATTI. *Minerva medica* [*Minerva med. (Torino)*] **1**, 58–63, Jan. 13, 1954. 1 fig., 33 refs.

The inhibitory action of salicylates on hyaluronidase has been attributed to liberation of heparin in the tissues, and favourable results have been reported from the administration of heparin and similar anticoagulants in the treatment of rheumatism. This effect of heparin has been attributed to an anti-exudative effect through osmotic and diffusional regulation, to its anticoagulant action diminishing antigen–antibody reactions, an anti-hyaluronidase action, or an anti-anaphylactic action. In this study, carried out at the Institute of Clinical Paediatrics, University of Genoa, three lines of inquiry were pursued: (1) the relative tolerance to heparin of rheumatic and non-rheumatic children; (2) the effect of hyaluronidase on clotting factors *in vitro*; and (3) the relation between hyaluronidase, heparin, and salicylate in regard to intradermal diffusion of coloured substances.

Heparin tolerance of non-rheumatic control patients and a group of 15 salicylate-treated rheumatic children was estimated by comparing the coagulation times at 10, 30, and 60 minutes after intravenous injection of 2,000 units of heparin. The non-rheumatic patients showed an average coagulation time of 37 seconds at 10 minutes, compared with 30 seconds in the rheumatic group. Since 5 non-rheumatic and 2 rheumatic patients had coagulation times of 50 seconds or over at 10 minutes, this estimation was used as a screening test for heparin treatment.

The effect of hyaluronidase on clotting factors *in vitro* was then investigated. Samples of blood from 10 children free from haematological disease were examined for prothrombin time (in the presence of progressive dilutions of thrombokinase), for recalcification time, and for antithrombin time, and the effect on these figures of distilled water and hyaluronidase in solutions of 25 and 1·25 units per ml. determined. Prothrombin and recalcification times were prolonged and the antithrombin time little affected. (As these results were similar to those obtained with heparin, the effects of a heparin–hyaluronidase mixture were not investigated.)

Lastly, the relation between hyaluronidase, heparin, and salicylate in regard to intradermal diffusion of coloured substances was investigated, mixtures of fluorescein and distilled water and fluorescein and hyaluronidase being viewed by ultraviolet light through Wood's glass in two groups of subjects—non-rheumatic children injected with heparin and rheumatic children under salicylate treatment. The figures for increase in areas of spread with hyaluronidase in non-rheumatic cases were 226 to 285 sq. mm., and with distilled water 178 to 224 sq. mm.; in the cases of rheumatism being treated with salicylates the figures were 215 to 264 sq. mm. with hyaluronidase, and 195 to 237 sq. mm. with distilled water. The authors suggest that these differences indicate that salicylate has a greater anti-hyaluronidase effect than heparin. [The differences, however, are not statistically significant.] *W. A. Bourne*

183. **Hormone Therapy in 22 Cases of Rheumatic Fever.** (Une expérience d'hormonothérapie dans la maladie de Bouillaud (22 cas))
B. GAUFROY. *Revue du rhumatisme et des maladies ostéo-articulaires* [*Rev. Rhum.*] **21**, 35–43, Jan., 1954. 1 fig.

184. **The Use of Cortisone and Hydrocortisone (Compound F) in Treatment of the Painful Shoulder**
M. B. COVENTRY. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **29**, 58–62, Jan. 27, 1954. 7 refs.

Encouraged by the good results obtained with cortisone in the treatment of 10 cases of periarthritis of the shoulder which had failed to respond to physiotherapy, the author extended this treatment to 50 similar cases, the results being reported in this paper from the Mayo Clinic. The drug was given by mouth in a dosage of 75 mg. a day for 3 to 4 weeks; in some cases, however, the dose was reduced to 50 mg. or less after the first week. Improvement was usually noted after the first 24 to 48 hours. Aspirin was given in addition if required. Manipulation was rarely necessary, but when it was performed cortisone was given after operation. The only side-effect was an exaggerated anxiety state in one patient. The author found that in general the more acute the periarthritis, the more satisfactory the result. In cases of calcific tendinitis, sprains, and degenerative changes in the long head of the biceps tendon and the musculo-tendinous cuff an injection of 25 to 50 mg. of hydrocortisone was given, repeated if necessary in 3 to 5 days.

It is concluded that in diffuse conditions, such as periarthritis, cortisone supplemented with physiotherapy is the most satisfactory treatment. For more localized conditions injection of hydrocortisone is the treatment of choice, acute calcific tendinitis responding particularly well, and sprains and degenerative conditions rather less satisfactorily. *H. F. Turney*

185. **Pseudo-polyarthritis of the Shoulder and Hip Girdles.** (Pseudo-polyarthrite rhizomélique)
J. FORESTIER and A. CERTONCINY. *Revue du rhumatisme et des maladies ostéo-articulaires* [*Rev. Rhum.*] **20**, 854–862, Dec., 1953. 4 refs.

To the syndromes classed as "inflammatory rheumatism" the authors add one which they name *pseudo-polyarthrite rhizomélique*. This account of the condition

is based on a study of 25 cases—17 in women and 8 in men. Pain in both shoulders, abrupt in onset and preventing by its extreme severity all movement at the joints, associated with a lesser degree of pain and stiffness in the hips, a low-grade fever, and some loss of weight are the most prominent clinical features of the syndrome, which affects individuals in the second half of life. It differs from the common scapulo-humeral periarthritis in being bilateral and symmetrical, and in its association with fever, loss of weight, raised erythrocyte sedimentation rate (E.S.R.), and pain and stiffness in the hips. It is not a form of rheumatoid arthritis, from which it differs strikingly in its localization exclusively to the roots of the limbs and in its evolution: there is no spread to other joints, the tendency being towards complete recovery with no residual signs. Also, by its clinical features and evolution it is readily distinguished from ankylosing spondylitis and from the shoulder–hand syndrome.

Treatment with copper and with gold has been tried. In cases of recent onset "cupralene" was given by intravenous injection in doses of 250 mg. twice weekly to a total of 2 to 3 g. Nearly all the patients so treated improved rapidly, the E.S.R. falling to normal within a few months. Others were treated, with equally good results, with "allochrysine" in doses of 100 mg. weekly to a total of 1 to 1·5 g. in each course, with an interval of 6 to 8 weeks between the courses. Improvement was marked during the first course; by its end, pain had disappeared, the E.S.R. was normal, and only some slight stiffness of the shoulder remained. In all cases, cure resulted after one or two courses.

[Information concerning the course of the untreated disease would be helpful.] *Kenneth Stone*

186. **A Comparison of Cortisone and Codeine Medication as an Adjuvant to Manipulation in Rheumatoid Arthritis**

SUBCOMMITTEE OF THE MEDICAL RESEARCH COUNCIL/NUFFIELD FOUNDATION JOINT COMMITTEE ON CORTISONE AND ACTH IN CHRONIC RHEUMATIC DISEASES. *British Medical Journal* [*Brit. med. J.*] **1**, 233–235, Jan. 30, 1954. 1 fig.

The purpose of the investigation here reported was to compare the effect of cortisone with that of compound codeine tablets (*B.P.*) in relieving the pain and curtailing the period of increased disability following the manipulation under a general anaesthetic of the flexed knees of patients suffering from rheumatoid arthritis. Four different centres took part, and 33 patients with flexion deformities of the knees of at least 6 months' duration were admitted to the trial, 18 receiving cortisone and 15 the tablets. To both groups the drug was given on the day before manipulation, on the day of manipulation, and for 14 subsequent days. The dose of cortisone was 200 mg. on the first day, 300 mg. on the day of manipulation and on the third day, 200 mg. on the fourth and fifth days, 150 mg. for the next 3 days, 100 mg. for the next 2 days, and 50 mg. for the last 6 days. Two compound codeine tablets were given 3 times a day to the other patients.

After manipulation the knee was put in plaster, which was bivalved after 24 hours, the posterior shell only being retained. Assessments of the patient's condition were made on the 5 days before and 5 days after manipulation, and then at 5-day intervals until the 26th day after admission to the trial. The assessments were all made by the same group of observers, and covered pain on pressure, pain on active and passive movement, range of movement, circumference of the knee, skin temperature, and the time taken to carry out complete flexion and extension 5 times with the heel supported on a skate in the horizontal position. From the results of the trial, which are given in the form of tables and a chart, it was concluded that "cortisone revealed no advantage over tab. codeine co. as a cover for manipulation of the knee".

[This report has evoked much discussion; it is important to note that the investigation was made only into the effect of these preparations on the sequelae of manipulation of a flexed knee, not into their effect on the disease as a whole.] *W. Tegner*

187. **An Evaluation of the Effects of Cortisone on the Subcutaneous Nodules of Patients with Rheumatoid Arthritis**

S. ZIVIN, I. E. STECK, M. M. MONTGOMERY, G. D. KAISER, and G. A. BENNETT. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **43**, 70–78, Jan., 1954. 9 figs., 17 refs.

This well-controlled study was carried out at the University of Illinois College of Medicine, Chicago, by means of clinical observation, measurement, and histological examination of biopsy specimens of the subcutaneous nodules of rheumatoid arthritis. It was shown that these nodules are commonly softened and reduced in size by the administration of cortisone, but that even over long periods of administration of the hormone there appeared to be no consistent modification of the histological picture. *A. C. Lendrum*

188. **Long Term Treatment of Rheumatoid Arthritis with *para*-Aminobenzoic Acid and Cortisone Acetate**

L. L. WIESEL and A. S. BARRITT. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **227**, 74–79, Jan., 1954. 15 refs.

In previous communications (*Brooklyn Hosp. J.*, 1950, **8**, 148, and *Amer. J. med. Sci.*, 1951, **222**, 243; *Abstracts of World Medicine*, 1951, **9**, 643, and 1952, **11**, 81) these authors have reported the synergistic action of *para*-aminobenzoic acid, given by mouth, and cortisone acetate, given by intramuscular injection. In this paper from the Brooklyn Hospital, New York, they report the effects of the combined oral administration, over a period of one year or more, of cortisone acetate and the sodium or potassium salt of *para*-aminobenzoic acid to 31 patients with rheumatoid arthritis. Their impression is that combination with *para*-aminobenzoate increases the anti-inflammatory action of a given dose of cortisone acetate two- to three-fold, and that such increased potentiation is not accompanied by a similar increase in the incidence of side-reactions or complications. *W. S. C. Copeman*

Neurology and Neurosurgery

189. **The Rehabilitation of Patients Totally Paralyzed below the Waist, with Special Reference to Making Them Ambulatory and Capable of Earning Their Own Living. V. An End-result Study of 445 Cases**
D. MUNRO. *New England Journal of Medicine* [*New Engl. J. Med.*] **250**, 4–14, Jan. 7, 1954. 2 refs.

The end-results of traumatic paraplegia have been surveyed in 445 patients who were treated at the Boston City Hospital and subsequently followed up for periods varying between a few hours and 25 years. All but 15 were injured in civil life. The site of injury was cervical in 207 cases, thoraco-lumbar in 114, lumbo-sacral in 51, and in the cauda equina in 73. The over-all mortality was 28%, while 81% of the survivors were considered to be fully able to care for themselves and 46% were fully or partially self-supporting. The author concludes that with proper care and rehabilitation, life expectancy is not materially altered by permanent paraplegia provided the patient has survived the injury for at least 18 months. The chief late complications are bed-sores, cystitis, and urinary calculi. Rehabilitation is not difficult, is of inestimable benefit to the patients, and is economically sound. In none of the patients were dislocated vertebrae wired together or otherwise tied by the spinous processes, laminae, or pedicles, and 2 who had been so wired elsewhere had their wires removed. Bed rest with hyperextension was the treatment employed until *x*-ray examination showed bony consolidation. This was followed by corrective therapy to encourage the maximum use of the muscles that remained active. The author considers that splints and operative fusion can be avoided with advantage to the patient: spinal fusion was not performed on these patients and plaster cases were not used.

[The high incidence of cervical lesions in this series is striking, as also is the author's opposition to fixation of the bony lesion—especially as in certain cases this would appear to make nursing easier in the early stages.]

Lambert Rogers

190. **The Cervical Cord in Multiple Sclerosis. Clinical Observations on the Local Spread of the Disease**
D. MCALPINE. *Archives of the Middlesex Hospital* [*Arch. Middx Hosp.*] **4**, 1–15, Jan., 1954. 5 figs., 20 refs.

Evidence of the involvement of the cervical segments of the spinal cord in the early stages of disseminated sclerosis was sought in the records of 150 patients who had been examined by the author at the Middlesex Hospital, London, within one year of the onset of the disease (an attack of retrobulbar neuritis was not counted as an initial attack in this connexion). It appeared that in 31 cases the cervical cord was the first part of the nervous system to show clinical involvement, that the initial symptoms were usually sensory, and that the posterior columns were first attacked in 25 of these cases. The author describes the mode of spread of paraesthesiae in four illustrative cases, and suggests that " symptoms are produced by a process of focal diffusion which may occur transversely across the cord and for some segments above and probably below the primary focus ". He discusses this idea in relation to the theory, first propounded by Williamson in 1903, that a " diffusing agent " is present in the early lesion of disseminated sclerosis.

J. W. Aldren Turner

191. **Osseous Changes in Myopathy**
J. N. WALTON and C. K. WARRICK. *British Journal of Radiology* [*Brit. J. Radiol.*] **27**, 1–15, Jan., 1954. 18 figs., 33 refs.

The skeletal changes observed on radiological examination in 38 cases of progressive muscular dystrophy, 17 of dystrophia myotonica, and 6 of myotonia congenita are described in this paper from the Royal Victoria Infirmary, Newcastle upon Tyne. In the patients with muscular dystrophy constant changes included narrowing of the shafts and rarefaction of the ends of the long bones, impaired development of flat bones, and coxa valga. Later, scoliosis appeared, with widespread decalcification and disorganization of cancellous structure, sometimes with gross distortion of the skeleton. The severity of the condition was related to age at onset and rate of progress. Similar changes were found in the wasted limbs of patients suffering from poliomyelitis. The authors believe that the osseous changes are related entirely to disuse, to the absence of normal stresses and strains, and to abnormal posture as a result of muscular weakness or contracture.

The bony changes in dystrophia myotonica, which were confined to the skull, consisted in thickening of the vault and a significantly smaller sella turcica, these changes becoming more marked with increasing age. There were no notable changes in the patients with myotonica congenita, all of whom were young. *Hugh Garland*

192. **Some Eye Defects Seen in Cerebral Palsy, with Some Statistics**
G. P. GUIBOR. *American Journal of Physical Medicine* [*Amer. J. phys. Med.*] **32**, 342–347, Dec., 1953.

Cerebral palsy may be associated with both oculomotor defects (such as conjugate deviation, convergent, divergent, or vertical strabismus, nystagmus, and fixation defects) and sensory visual disturbances (such as amblyopia or field defects). The principal types of disturbance of the eye movements, which may be noticed before any disability of the limbs is detected, are: (1) conjugate deviation with no recovery; the eyes may eventually be unable to move in the direction opposite to that of the conjugate deviation, and the patient may turn his head to compensate for the defect of movement or to avoid nystagmus and blurred vision, which occur on attempting to look straight forward; (2) conjugate deviation with partial recovery, that is, no deviation when the gaze is

directed straight ahead, but poor movement when looking to the affected side; (3) primary conjugate deviation overcome by the patient's learning to fix with one eye, resulting in unilateral strabismus and amblyopia; and (4) a divergent squint of one eye, which later becomes alternating, caused by a lesion of the midbrain.

Among 142 children with cerebral palsy examined at St. Luke's and the Children's Memorial Hospitals, Chicago, the following were the most common ocular defects encountered: esotropia (51%); pseudopalsy externi (22·5%), the elongation of the external recti being secondary to contracture of the adductors; horizontal conjugate gaze defects (33%); and synkinetic overaction of the inferior oblique muscles (9·5%). Operation to correct such defects should be delayed until about the age of 8 so as to allow for possible recovery; needless to say, the response to treatment is not so good as in similar cases without cerebral palsy. The author draws attention to the similarities between spastic esophoria and the spastic type of cerebral palsy. *J. Foley*

193. **Dimercaprol in the Pre-neurological Stage of Wilson's Disease (Hepatolenticular Degeneration)**
C. G. WARNOCK and D. W. NEILL. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] **17**, 70–74, Feb., 1954. 1 fig., 24 refs.

A pre-neurological case of Wilson's disease is described and its progress during 4 years of treatment with dimercaprol is recorded. Almost all evidence of hepatic dysfunction has disappeared and nervous symptoms are still absent. Clinical and diagnostic problems associated with the disease at this stage are discussed.—[Authors' summary.]

194. **Chain-synergies in Neuromuscular Re-education in the Infantile Cerebral Flaccid-spastic Syndrome**
A. OBHOLZER. *South African Medical Journal* [*S. Afr. med. J.*] **28**, 105–110, Feb. 6, 1954. Bibliography.

The author, writing from the School for Physically Handicapped Boys, Kimberley, South Africa, states that in the past the orthodox treatment of patients with cerebral palsy has concentrated on teaching the patient to contract individual muscles. He points out that this is difficult enough for the normal adult to perform, but that for children with cerebral palsy, 45% of whom are mentally defective, the procedure is almost impossible. In addition, it is known that movements and not muscles are represented in the cerebral cortex; moreover, functionally, the contraction of individual muscles has no practical use.

The author reviews the literature on past and present ideas of rehabilitation from a neurological and re-educational viewpoint. The present-day re-educational trends are based on two principles: (*a*) the use of reflexes, and (*b*) " developmental ideas ". It is in the first group that the " chain-synergy " treatment here described is placed. As its name implies, it is a mass or compound movement of several joints as a result of the action of a chain of synergistic muscles. This is demonstrated in hemiplegic patients as Strümpell's phenomenon (described by him in 1887), and is the basis for the resistance treatment advocated. The physiotherapist and occupational therapist play important roles in this type of resistance treatment, in which the aim is to attain the required movements through tasks both purposeful and enjoyable to the patient. *J. B. Millard*

BRAIN AND MENINGES

195. **Localization of Intracranial Neoplasms with Radioactive Isotopes**
W. B. SEAMAN, M. M. TER-POGOSSIAN, and H. G. SCHWARTZ. *Radiology* [*Radiology*] **62**, 30–36, Jan., 1954. 3 figs., 13 refs.

The authors report their findings in 200 cases of suspected cerebral tumour which were investigated at the Washington University School of Medicine, St. Louis, by the method of determining the point of greatest radioactivity after the intravenous injection of diiodofluorescein containing radioactive iodine (^{131}I). The first 22 patients were studied by means of a bismuth-coated cathode Geiger tube, 1 mc. of the isotope being injected intravenously, but in the remaining patients a scintillation counter, which is much more sensitive, was used and a dose of 0·25 mc. was then adequate. The authors' method is as follows. After the injection, the counter is centred on the zygoma and kept there until the counting rate reaches a plateau, usually in about 15 to 20 minutes. A routine survey at 32 positions on the skull (that is, at 13 symmetrical points on each side and 6 in the mid-line) is then made. As the rate of counting is very high it is necessary to count only 15 to 20 seconds at each area, thus making possible a complete survey of the skull in 30 or 40 minutes. A difference greater than 10% between the rates of count in any two symmetrical areas was considered significant, provided it could be obtained on repetition.

Of the 200 cases, 85 were confirmed at operation or necropsy. The lesion had been correctly located in 30 (46%) of 65 patients with tumour, and of the 20 non-neoplastic cases (haematoma, aneurysm, or abscess), 10 (50%) were correctly located. In the authors' experience the greatest difficulty was in locating subtentorial tumours, only 3 out of 11 posterior fossa tumours being accurately located, but the accuracy rate for supratentorial tumours was 50%.

In discussing this method of location the authors point out that detection depends on the proximity of isotope concentration to the radiation detector. Hence, deeply placed and small tumours are likely to be missed unless they have a high absorption ratio for the isotope. Biological factors, such as necrosis or cyst formation in the tumour, result in little or no isotope concentration. Reviewing the tumours which could not be located, the authors found about two-thirds of them showed physical or biological characteristics that could account for the failure. It has been suggested that the differential retention of diiodofluorescein is a function of the degree of cellularity of the tumour, but histological study of the verified tumours in this series showed no striking correlation between cellularity and success or failure in

location. The authors conclude that the clinical status of this test is yet to be definitely determined, but believe that it may prove to be a useful screening procedure in the selection of patients for further diagnostic studies.

J. V. Crawford

196. **The Relationship of Oxygen Consumption to Cerebral Functional Activity**

J. M. GARFUNKEL, H. W. BAIRD, and J. ZIEGLER. *Journal of Pediatrics* [*J. Pediat.*] **44**, 64–72, Jan., 1954. 34 refs.

197. **Metabolic Disorders in Head Injury. Survey of 76 Consecutive Cases**

G. HIGGINS, W. LEWIN, J. R. P. O'BRIEN, and W. H. TAYLOR. *Lancet* [*Lancet*] **1**, 61–67, Jan. 9, 1954. 17 refs.

The metabolic disorders in 76 patients with closed head injury who remained unconscious for more than 12 hours were studied at the Radcliffe Infirmary, Oxford. During the first 12 hours the patients received no fluids except intravenous blood transfusion, if indicated. After 12 hours, tube-feeding was begun with a high-calorie diet adequate in protein and vitamins, the water and salt content being adjusted to metabolic requirements. No biochemical abnormality was noted in 8 of the patients. In 50 patients there were transient disorders including: a rise in the blood urea level (to a peak in some cases of 50 to 70 mg. per 100 ml.), which was generally extra-renal in origin; a small reduction in total plasma protein level; hyperglycaemia and glycosuria; renal glycosuria; and proteinuria.

Major metabolic disorders were observed in the remaining 18 patients as follows. (1) Hyperchloraemia with hypochloruria was present in 9, only one of whom had hyperglycaemia. The urinary excretion of sodium paralleled that of chloride in the 5 cases in which these values were determined. At necropsy in 5 cases in this group the kidneys were found to be normal, but there was contusion of the under-surface of the frontal lobes of the brain. There was no evidence of dehydration or reduction in blood volume in the patients in this group, and pyrexia was not a constant feature. (2) An increase in the sodium and chloride content of the urine, with hypochloraemia and hyponatraemia and clinical evidence of salt deficiency, were observed in 5 patients. This syndrome usually developed in the second week. A high-sodium diet and administration of deoxycortone acetate and cortisone failed to raise the plasma sodium and plasma chloride levels, although the hormones produced oedema in 2 cases. Post-mortem examination in one case revealed normal kidneys. (3) Water deficiency due either to inadequate fluid intake before admission or to deliberate dehydration to reduce intracranial pressure developed in several patients. The clinical features were dry mouth and tongue, loss of skin turgor, and low intra-ocular pressure. Other findings were raised serum sodium and plasma chloride levels with urinary levels of sodium and chloride in excess of 17 mEq. per litre. (4) Hyperpnoea, respiratory alkalosis, and muscular irritability were observed in 2 patients. (5) A high blood urea level with a low urinary urea concentration was found in 3 patients, all of whom died [the renal lesions in these cases are not specified].

It is suggested that metabolic disorders play a part in causing death in cases of head injury, and that their prevention or correction should help to reduce the mortality.

K. G. Lowe

198. **Coagulability of the Blood and Cerebral Vascular Accidents.** (Coagulabilité sanguine et accidents vasculaires cérébraux)

D. MAHOUDEAU, S. DAUM, and J. DUBRISAY. *Presse médicale* [*Presse méd.*] **62**, 262–264, Feb. 20, 1954. 2 figs., 2 refs.

In this paper the authors report the results of a study of blood coagulability and of the heparin tolerance test performed *in vitro* in 89 cases of cerebrovascular accident.

A state of hypercoagulability of the blood was found to be present on the first day in many cases of cerebral thrombosis and embolism, but in no case persisted longer than the second or third day. This state of hypercoagulability was commonly succeeded by a reactive change to one of hypocoagulability which, though ephemereal in cases of cerebral embolism, was of considerable duration in the thrombotic cases. The authors consider that this state of " reactive hypocoagulability " may be responsible for the conversion of some simple thrombotic and embolic lesions into severe infarctions, accompanied by haemorrhage or extensive oedema. They therefore urge great caution in the use of anti-coagulants in cases of cerebrovascular accident. They believe that, although occasionally indicated in cerebral embolism, these substances are almost never justified in cerebral thrombosis. They urge that in all cases the results of laboratory tests must be the guide to treatment.

P. D. Bedford

199. **Surgical Treatment of Saccular Intracranial Aneurysms. A Report of 56 Consecutively Treated Patients**

H. F. STEELMAN, G. J. HAYES, and H. V. RIZZOLI. *Journal of Neurosurgery* [*J. Neurosurg.*] **10**, 564–576, Nov., 1953. 6 figs., 5 refs.

In this paper the authors report their combined results in the surgical treatment of intracranial aneurysms, it being considered that " the approach to the problem has been similar enough to make the series homogeneous ". Of the 56 aneurysms reported, 41 were of the internal carotid artery (21 sub-clinoid and 20 supra-clinoid), only 15 being more peripherally placed. The mortality of operation was 3·6% (2 deaths), and 4 patients (7%) developed a postoperative hemiplegia. The authors favour direct intracranial attack where no contra-indication exists.

[The case for such direct attack has not been incontrovertibly made here, for 21 of the 56 aneurysms were sub-clinoid, a type which is but rarely associated with subarachnoid haemorrhage and which responds well to simple cervical carotid ligation. Further, of the remaining 35 cases in the series, 20 were supra-clinoid aneurysms of the internal carotid artery—a type which again frequently lends itself to treatment by carotid ligation.

The need for intracranial procedures in the majority of patients with aneurysms of either of these types has yet to be convincingly demonstrated.] Of the 15 more peripheral aneurysms, 2 were treated by carotid ligation and 13 by an intracranial operation with one post-operative death and one hemiplegia.

J. E. A. O'Connell

CRANIAL NERVES

200. The Neurological Importance of Tumours of the Glomus Jugulare

E. R. Bickerstaff and J. S. Howell. *Brain* [*Brain*] **76**, 576–593, 1953. 7 figs., 45 refs.

The authors, writing from the University of Birmingham, describe the clinical manifestations of tumours arising from the glomus jugulare, analyse 87 cases from the literature, and present 3 personal cases. Cases were divided, according to the time elapsing between the onset of aural and neurological symptoms, into four groups, the largest group (49 cases) presenting with aural symptoms alone, the smallest group (4 cases) showing involvement of the cranial nerves, and the other two groups intermediate stages.

The authors stress that to the neurologist the crucial factor in diagnosis is the association of unilateral cranial-nerve palsies with an aural growth which, in the majority of cases (72%), bleeds either spontaneously or in response to operative interference, sometimes almost uncontrollably. In the vast majority of cases (86 out of the 90) the earliest symptoms were aural, consisting in the main in unilateral increasing deafness and tinnitus. In 10 cases the tumour was associated with a coexistent tumour, occasionally bilateral, of the carotid body. An audible bruit was present in a further 10 cases, and in 8 a pulsatile mass below the mastoid or behind the ear was the presenting sign.

Early diagnosis is important, since surgical eradication may be possible if undertaken before neurological signs develop. At a later stage, deep *x*-ray therapy may bring about some amelioration of symptoms.

Fergus R. Ferguson

201. Treatment of Trigeminal Neuralgia with Vitamin B_{12}

S. J. Surtees and R. R. Hughes. *Lancet* [*Lancet*] 1, 439–441, Feb. 27, 1954. 1 ref.

In 1952 Fields and Hoff (*Neurology*, **2**, 131; *Abstracts of World Medicine*, 1952, **12**, 265) reported the successful use of large doses of vitamin B_{12} in the treatment of trigeminal neuralgia, and in the present paper the authors describe the results obtained at the Royal Southern Hospital, Liverpool, in 18 cases of trigeminal and one of glosso-pharyngeal neuralgia. Patients treated early in the investigation were given an intramuscular injection of 1,000 μg. of vitamin B_{12} twice a week, to a total of 5 injections. No toxic effects were noted. Later patients received 1,000 μg. daily for 10 days followed by 1,000 μg. twice a week for 5 injections. Some patients received as much as 1,000 μg. twice daily for 3 weeks without apparent harm. In 15 of the 19 patients there was " considerable improvement or complete relief of pain ", in one " moderate improvement ", and in 3 " little or no immediate improvement ". Most of the patients who showed improvement experienced complete relief of pain after one or two injections; in others the neuralgia subsided slowly. Some patients were given a maintenance dose up to 1,000 μg. a week for recurrence of pain, but the majority received no further treatment. The longest follow-up period was 7 months.

The authors conclude that while vitamin B_{12} can produce a remission which may last a long time, there is no evidence that it will permanently cure trigeminal neuralgia.

Donald McDonald

202. Decompression of Ganglion and Posterior Root of Fifth Nerve for Trigeminal Neuralgia

D. Cleveland and E. J. Kiefer. *Archives of Otolaryngology* [*Arch. Otolaryng. (Chicago)*] **59**, 30–35, Jan., 1954. 11 refs.

In discussing measures for the relief of trigeminal neuralgia the authors point out that the great disadvantage of resection of the posterior root of the 5th nerve is the danger of keratitis if the first division is lost. When pain is limited to the second and third divisions many surgeons prefer to perform differential section of the posterior root, but even so, patients may find the resulting anaesthesia annoying. Division of the descending tract of the 5th nerve in the medulla (" trigeminal tractotomy ") abolishes pain perception but leaves tactile sense; this operation, however, is more dangerous than root division, being followed in some cases by ataxia and disturbances in coordination. Resection or nerve block peripheral to the ganglion gives only temporary relief.

In 1952 Taarnhøj (*J. Neurosurg.*, 1952, **9**, 288) described good results from a method of decompression of the ganglion and posterior root by widely opening the dural sheath without division of any fibres, one advantage of this procedure being that, should pain return, it is simple to divide the posterior root later. The present authors have modified this approach and open the dura up to the pons. They have now treated 22 cases of trigeminal neuralgia in this way, with complete relief in all except one, in which it was necessary to divide the root at a second operation. The operation is usually followed by temporary anaesthesia in small scattered areas.

There seems to be as yet no explanation as to how the beneficial results are obtained. As the authors point out, it cannot be a real " decompression result " because sometimes the pain, although immediately diminished, does not entirely cease for several days; nor can it be due to division of the " trigger fibres " among stray fibres attached to the dura, as in many cases there was no loss of sensation in the trigger zone. In some cases a small artery was found coursing over the root, but in no case was there any evidence of it causing pressure. It may be that the operation alters some circulatory or cerebrospinal-fluid effect which is responsible for the attacks.

F. W. Watkyn-Thomas

Psychiatry

203. **A Survey of Patients in Twelve Mental Deficiency Institutions**
N. O'CONNOR and J. TIZARD. *British Medical Journal* [*Brit. med. J.*] **1**, 16–18, Jan. 2, 1954. 4 refs.

In this paper from the Medical Research Council Unit for Research in Occupational Adaptation the results are reported of a survey of a 5% sample of the patients in mental deficiency hospitals in the counties of Kent, Surrey, and London. A set questionary was answered by reference to case papers and records, supplemented by information obtained from senior members of the nursing staff. The survey included 592 patients (the total number in the institutions was 11,850), 40% of whom were classified as imbecile and less than 5% as idiot. Of the 73 children (12·3%) included, 43 were boys and 30 girls, mostly low-grade mental defectives. Of the adults 58% were classified as feeble-minded, and most of these were under 50 years of age. A total of 54 patients were on resident licence from the institutions, while 21 were on daily licence. The use of locked wards varied considerably between the institutions. Of the 538 resident patients 75 (13%) were on day parole during the month preceding the investigation and 123 went on leave during the preceding year. About 50% of patients did not need special nursing or supervision, while 24% needed close supervision but no special nursing.

The rewards and "wages" to patients were partly in kind, partly in money: 42% received an equivalent of 1/- or less per week, 13% one of 5/-, and 2% one of 16/- or more. The majority of patients who were working were in domestic service, some inside the hospital and some outside. Only one institution made a practice of sending patients to work in a factory. Measurement of intelligence by the progressive matrices test in the 49 feeble-minded patients between 16 and 29 years who were available, indicated that the average I.Q. was above 70. General behaviour of the resident patients was apparently good, but 3% had absconded at least once during the preceding year. *E. H. Johnson*

204. **Vomiting in Pregnancy. A Psychiatric Study**
W. A. HARVEY and M. J. SHERFEY. *Psychosomatic Medicine* [*Psychosom. Med.*] **16**, 1–9, Jan.–Feb., 1954. 12 refs.

At the New York Hospital (Cornell University Medical College) a group of 20 unselected patients with persistent vomiting in pregnancy severe enough to justify admission were subjected to psychiatric examination, and the results compared with those of a similar examination of 14 women entirely free from any complaint of nausea throughout pregnancy. In the former group, 19 patients gave a clear history of previous gastrointestinal disorders of which vomiting was a feature, and vomiting as a response to stress was often mentioned; only 2 of the 14 control subjects had any history of similar gastrointestinal complaints, and these 2 had experienced mild anorexia with menstruation. All of the patients with vomiting were of an over-anxious disposition, and 3 had suffered from depressive illnesses; all showed overt anxiety and tension during, and for some time after, the period of vomiting. Three of the control subjects were unusually tense, but the remainder went through pregnancy contentedly. Frigidity was present in all the patients with vomiting (though in 4 cases it lasted only as long as the pregnancy), 10 complained of dyspareunia, and 10 of precipitation of vomiting by coitus. Of the control subjects, 2 had experienced frigidity earlier in their lives, and one complained of nausea during coitus later in pregnancy. The women who suffered from severe vomiting were in general immature, dependent, rather passive, and compliant, though there was much variation in personality pattern.

[These findings are in accord with Robertson's observations on the correlation of gastrointestinal symptoms in pregnancy with aversion to coitus (*Lancet*, 1946, **2**, 336).] *Desmond O'Neill*

205. **Some Psychosomatic Aspects of Food Allergy**
W. KAUFMAN. *Psychosomatic Medicine* [*Psychosom. Med.*] **16**, 10–40, Jan.–Feb., 1954. 10 figs., bibliography.

In a lengthy and interesting paper the author discusses the interrelation of allergenic and psychogenic factors in the causation of reactions to food. For example, some patients who are allergic to a particular food will at times experience a strong unconscious need to consume this very article, although they are aware that it will make them ill. Such self-inflicted illness may be very puzzling unless the physician is able to comprehend the patient's psychodynamics as well as his physical state.

[There is much material in this paper which is difficult to render in abstract form.] *Desmond O'Neill*

206. **Clinical Outcome in General Paralysis of the Insane and Taboparesis**
M. WHELEN and M. H. BREE. *Lancet* [*Lancet*] **1**, 70–74, Jan. 9, 1954.

The object of the investigation described in this paper was to determine whether certain auxiliary factors, over and above the reversibility of the cerebral damage and the adequacy of treatment, influence the clinical outcome in cases of general paralysis of the insane and taboparesis. From a total of 536 patients who were well enough to be discharged from Horton Hospital, Surrey, the authors selected 132 who had been followed up for at least 5 years. Most of them had received malaria therapy only. It was found that 39 of the 132 patients had recovered completely, apparently as the direct result of treatment, the majority of them within a period of 2 years. Improvement, varying in degree, was observed in 81 patients over a mean 5-year period, and

in this group the influence of extraneous factors—a good personality before the illness, a dependable and sympathetic " prop ", usually a close relation, and an occupation, not necessarily gainful, within the patient's capacity—was most apparent. The remaining patients, whose condition was stationary, lacked one or more of these factors. The authors suggest that these factors function " by providing facilities for stimulating and re-educating the damaged nervous system in a personality able to profit by them ". *A. C. Tait*

207. **Electrotonic Treatment in Dementia Paralytica**
M. C. PETERSEN. *Journal of Nervous and Mental Disease* [*J. nerv. ment. Dis.*] **118**, 162–167, Aug., 1953. 3 refs.

During the 7-year period 1943–50, 70 patients with dementia paralytica received electric convulsion therapy at the Rochester (Minnesota) State Hospital, a total of 1,120 treatments being given, usually with curare. The condition of 42 patients was much improved, and 21 others showed some improvement. The treatment—which was always followed by chemical or fever therapy or both—was not used primarily for the underlying pathological condition, but it is claimed that it greatly eases the management of disturbed patients, and may be life-saving. The only complication encountered in this series was status epilepticus, easily terminated, in one case. In the majority of patients who had not recently received intensive treatment the cell count and protein content of the cerebrospinal fluid decreased, possibly owing to an improvement in cerebral circulation or to stimulation of the immunological mechanisms of the body.

A. C. Tait

208. **Results of Psychiatric Treatments with a Control Series. A 25-Year Study**
E. D. BOND. *American Journal of Psychiatry* [*Amer. J. Psychiat.*] **8**, 561–566, Feb., 1954.

The results of psychiatric treatment of 393 patients with schizophrenia admitted consecutively to the Pennsylvania Hospital, Philadelphia, between 1925 and 1934—that is, before the introduction of insulin shock and electric convulsion therapy—are compared with the results obtained in 440 cases admitted between 1940 and 1945, when shock treatment was available, though not necessarily given to all the patients. Results in both groups were assessed 5 years after admission. Recovered and much improved patients are classified together and designated " satisfactory results ". Almost one-tenth of the first group and nearly one-fifth of the second group were untraced 5 years after admission [this is largely disregarded in the evaluation]. " Satisfactory results " were obtained in 13% of the patients in the first group and in 29% of those in the second. In both groups the number of satisfactory results was higher among patients who had been ill for less than 18 months before admission than in those who had been ill for a longer period.

The author, who has been associated with the Pennsylvania Hospital since 1913, argues that in the 25 years from 1925 to 1949 there was little or no change in hospital conditions or in diagnostic criteria in cases of schizophrenia, so that the difference between the two groups must be attributed to the availability of shock therapy.

[Had the author used statistical methods for evaluating the results he would have found that they were highly significant, even if all the untraced patients were regarded as failures.] *F. K. Taylor*

209. **Prognosis of Depression Treated by Electric Convulsion Therapy**
H. F. JARVIE. *British Medical Journal* [*Brit. med. J.*] **1**, 132–134, Jan. 16, 1954. 1 fig., 2 refs.

The author reports the results of a 3-year follow-up investigation of 114 patients treated at Cheadle Royal Hospital, Cheshire, between May, 1947, and April, 1949, for a " typical " depressive illness. Most of the patients belonged to the Registrar-General's social classes I and II, and more than half of them were over 50 years of age. All except 17 of the patients received electric convulsion treatment (E.C.T.). Of the treated patients 71 were discharged as recovered after an average of 7 treatments (range 2 to 14) and an average stay in hospital of 7 weeks. At the end of the 3-year period 25 of these 71 patients were completely well, 9 were fairly well, 25 had suffered a relapse (generally within 6 months to a year after discharge), 5 had died, and 7 were untraced. The remaining 26 treated patients were discharged as improved after an average of 7·5 treatments and an average stay in hospital of 8 weeks. Only 4 of these 26 were well at the end of the follow-up period; the condition of 6 was " the same as on discharge "; 4 were " unwell " after E.C.T. therapy for a relapse; 3 had undergone leucotomy; 2 had died; and 7 were untraced. Epileptic seizures developed in one patient who had received 60 treatments over a period of 5 years.

The author concludes that E.C.T. is an effective form of treatment in most cases of depression, but that its limitations in some 30 to 40% of cases should be recognized. *F. K. Taylor*

210. **A New Preparation with Elective Action in Delirium Tremens.** (Su di un recente farmaco ad azione elettiva nel " delirium tremens ")
A. CUNEGO. *Neurone* [*Neurone*] **1**, 261–273, 1953. 16 refs.

The author describes the results obtained at the Provincial Psychiatric Hospital, Verona, in the treatment of 25 alcoholics by a method similar to that developed by Bruel and Lecoq, consisting of intravenous injections of " etilcure ", a preparation composed of isotonic glucose-saline containing 12 ml. of absolute alcohol (99·9%) and 100 mg. of nicotinic acid in each 50 ml. The dosage ranged from 180 ml. (in two separate injections) on the first day to 50 ml. daily by the end of the first week. The author has found this treatment highly satisfactory, especially in cases with mental disturbance, delirium tremens, and pre-delirium confusional states. There were no deaths in his series and no undesirable side-effects. The method is intended for the more acute episodes of alcoholism, and in some of the author's cases treatment was continued with disulfiram. The mode of action of etilcure is discussed. *J. B. Stanton*

Dermatology

211. **The Effect of Topical Application of Vitamin A with Special Reference to the Senile Skin.** [In English] F. Reiss and R. M. Campbell. *Dermatologica* [*Dermatologica (Basel)*] **108**, 121–128, Feb., 1954. 4 figs., 24 refs.

The effects on various skin disorders of the local application of ointments containing vitamin A was studied by the authors at the Montefiore Hospital, New York, the ointment base being applied to a control area of skin at the same time. The vitamin ointment appeared to produce clinical and histological improvement in 4 patients with senile skin changes (xerosis, scaliness, and moderate atrophy) over and above that caused by the base itself. There was some improvement in a variety of other scaling dermatoses, but not in psoriasis. *John T. Ingram*

212. **Sodium Sulfacetamide in Topical Therapy**
W. W. Duemling. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph. (Chicago)*] **69**, 75–82, Jan., 1954. 1 fig., 8 refs.

The author reports good results from the use of sodium sulphacetamide in the treatment of "pyococcic" and seborrhoeic dermatoses. An ointment containing 10% of sodium sulphacetamide in an oil-in-water type of base, and a shampoo containing 3% of the drug in a soapless liquid detergent completely controlled 46 and much improved 25 out of 76 cases of seborrhoeic dermatitis. Among 24 other cases treated, 4 out of 5 cases of otitis externa were completely controlled. Unfavourable reactions were extremely rare. *J. E. M. Wigley*

213. **Changes in the Skin following the Local Application and Injection of Hydrocortisone Acetate.** (Modifications cutanées consécutives aux applications et aux injections locales d'acétate d'hydrocortisone)
E. Sidi and J. Bourgeois-Gavardin. *Presse médicale* [*Presse méd.*] **61**, 1760–1763, Dec. 25, 1953. 18 figs., 11 refs.

An investigation was carried out at the Rothschild Ophthalmological Hospital, Paris, into the effect of the local application of a cream containing hydrocortisone acetate (10 to 25 mg. per g.) on certain dermatoses. The technique has been described in an earlier article (*Presse méd.*, 1953, **61**, 992). Of 16 patients with marked localized pruritus, 6 were cured and 8 were improved; relapses were frequent, but maintenance treatment proved effective. Intense lichenification prevents absorption and hence reduces the effect of the cream. Very good results were obtained in 16 cases of palpebral eczema, and 15 out of 18 cases of weeping eczema also responded well, but excessive crusting of the lesions proved troublesome. Seborrhoeic eczema also responded well, but relapsed when treatment was stopped. Little or no permanent effect was obtained in 7 cases of lupus erythematosus. The frequency of relapse after treatment and the excessive drying up are the main disadvantages of this cream; the latter is certainly partly attributable to the cream base.

Local injections of 0·125 to 0·25 ml. of a solution of hydrocortisone acetate containing 25 mg. per ml. were also given intradermally and subcutaneously to 5 patients with lupus erythematosus. The injections were somewhat painful, but had a distinctly better effect than the cream. Keloids were treated by local injection in 6 cases, and although no cure has yet been obtained, the results have been such as to justify perseverance with the treatment.

In a study of the influence of hydrocortisone acetate on skin sensitivity reactions, the authors attempted by means of applications of the cream to inhibit the skin responses of patients sensitized to various substances such as penicillin and procaine, but the results were equivocal, and no conclusions could be drawn from them. The local injection of hydrocortisone acetate on the other hand did completely prevent a skin reaction in 10 cases and partly prevented it in 7 others in which a very strong reaction had been obtained previously. It is possible, however, that the skin reaction is prevented physically by the saturation of the tissues with microcrystals, a point which is being investigated by the study of tissue sections. *Ferdinand Hillman*

214. **Dermatological Changes in Hypocalcaemia**
J. A. Simpson. *British Journal of Dermatology* [*Brit. J. Derm.*] **66**, 1–15, Jan., 1954. 9 figs., bibliography.

The author reports, from the Western Infirmary, Glasgow, the dermatological changes observed in 34 cases of hypocalcaemia of which 5 were due to hypoparathyroidism and 29 were associated with steatorrhoea. Although the condition is not uncommon, these cases are thought to be worth reporting since in some of them the changes in the skin, nails, and hair preceded other clinical manifestations, so that their significance was not appreciated until tetany ensued. The literature on the subject is reviewed.

Acute hypocalcaemia causes temporary disturbance of growth of ectodermal tissue, resulting in shedding of the hair, transverse grooving of the nails, and possibly furrowing of the developing dental enamel. These changes are more likely to be present if tetany occurs, though carpo-pedal spasm may be absent. It is suggested that angiospasm and increased capillary permeability may be responsible for these changes.

Chronic hypocalcaemia is a more difficult problem, since nutritional deficiencies, whether primary or secondary to malabsorption as in steatorrhoea, tend to be multiple, though "pure" calcium deficiency is seen in hypoparathyroidism. In that state the most constant changes are dryness, puffiness, scaliness, and pigmenta-

tion of the skin, brittleness with longitudinal striation of the nails, and scantiness of the hair of the scalp, eyebrows, and axillae. Many of these features are also seen in steatorrhoea. The author suggests that prolonged calcium deficiency may block enzymatic processes and interfere with the integrity of cell membranes.

Secondary infection of the affected skin or nails may occur, the nails being thought to be more prone to mycotic infection than normally, and one such case, the only one in the series, is described. *S. T. Anning*

215. **On Elastase and the Elastic Dystrophies of the Skin**

G. H. FINDLAY. *British Journal of Dermatology* [*Brit. J. Derm.*] **66**, 16–24, Jan., 1954. 4 figs., 20 refs.

The author, working at the University of Pretoria, South Africa, has attempted to elucidate some aspects of elastolysis and to apply his findings to the study of some elastic dystrophies of the skin. [For techniques and experimental details the original paper should be consulted.] He has shown that when normal or abnormal elastic tissue is digested by elastase in tissue sections, fibres which are morphologically identical show a variable susceptibility to the enzyme. Certain general trends can, however, be established. For example, in the degenerative diseases the fibre first toughens. Thus, in the elastorrhexis and elastoclasis of pseudoxanthoma elasticum and also in the elacin of senile elastosis there is increased resistance of elastic fibres to elastase. But later, in the colloid change in senile elastosis and in colloid milium, there is facilitation of elastolysis.

S. T. Anning

DERMATITIS

216. **Oxytetracycline–Polymyxin B Ointment in Skin Infections**

B. APPEL. *Antibiotics and Chemotherapy* [*Antibiot. and Chemother.*] **3**, 1258–1267, Dec., 1953. 2 figs., 9 refs.

The author reports clinical observations on the effect of an ointment containing 3% oxytetracycline and 0·1% polymyxin-B sulphate in a petrolatum base in cases of skin infection at the Boston City Hospital (Tufts College Medical School). The rationale of the treatment is to combine the wide antibiotic spectrum of oxytetracycline against streptococci, staphylococci, and the coliform group with the effectiveness of polymyxin B against the coliform group and against *Pseudomonas aeruginosa* and other *Pseudomonas* organisms.

A series of 200 patients with various skin infections were treated, the ointment being applied 3 times daily after crusts had been removed with a detergent. No case of dermatitis venenata due to irritation or sensitization was observed. The ointment was strikingly effective in cases of pyogenic dermatosis: all 21 cases of impetigo cleared up in 2 to 10 days, and of 18 cases of folliculitis of the scalp, beard, or axilla 15, including long-standing cases, cleared up completely and 3 were very much improved. Details are given of some of the 54 cases of impetiginized dermatosis treated, which included 10 of disseminated neurodermatitis, 20 of dermatitis venenata, 8 of seborrhoeic dermatitis, 4 of hypostatic dermatitis and varicose ulcer, 3 of herpes simplex, and 9 of miscellaneous dermatoses. In all the cases the superinfection responded rapidly, although the underlying dermatosis was not usually affected. Treatment was effective in 3 to 5 days in 5 cases of otitis externa of 1 to 5 months' duration, and in 3 to 8 weeks in 5 cases of acne necrotica miliaris of the scalp of 5 months' to 3 years' duration. Treatment was ineffective in 2 cases of pyogenic granuloma, 6 of chronic pustular acrodermatitis (pustular psoriasis), and cases of exudative discoid dermatitis, sickle-cell leg ulcer, palmar psoriasis, erythema multiforme, dermatophytosis, and neurodermatitis circumscripta.

The ointment was also used as a dressing after minor surgical procedures in 56 cases. In all of these the wounds healed without any evidence of infection.

The author concludes that topical application of a mixture of oxytetracycline and polymyxin B is a safe and effective method of treating skin infections.

Benjamin Schwartz

217. **Chancriform Pyoderma**

C. W. LAYMON, C. BALOGH, and A. DIXON. *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [*Amer. J. Syph.*] **38**, 57–62, Jan., 1954. 2 figs., 5 refs.

After a brief review of the few cases of pyoderma simulating syphilitic chancre reported in the literature, the authors discuss the condition of chancriform pyoderma. Clinically this lesion, which is almost always solitary, presents as a button-shaped ulcer or erosion, usually superficial rather than deep, with an indurated base and an eroded, circular, usually bright red border. The secretion is more often serous than purulent, and the lesion may become covered with a yellow or dark crust. There is a characteristic associated firm, indolent lymphadenitis.

Children are affected more commonly than adults. The lesion is usually found on the face, hands, or genitals, and may occur especially on delicate skin such as the eyelids and lips. When the genitals are involved, ulceration may be deep and perforating. Dark-field examination for *Treponema pallidum* is negative and Guarnieri bodies are not found. Histological examination shows non-specific inflammatory changes. The lesions soon heal with treatment similar to that for impetigo, but may leave scars, depending on the depth of the original ulceration. The lymph nodes rapidly return to normal. Solitary recurrences may occasionally appear after several months in areas near the original lesion.

The authors describe in detail 2 cases seen recently at Minneapolis General Hospital. In the first patient, a man of 70, the lesion occurred on the ventral surface of the penis and was 1·5 cm. in diameter. The second patient, a man of 46, had a shallow ulcer 0·75 cm. in diameter on the chin. In both cases serological tests for syphilis were negative; cultures from the ulcer yielded a growth of haemolytic streptococci in the first case and of *Staphylococcus albus* in the second.

The differential diagnosis from syphilis, tuberculosis, " accidental vaccination ", chancroid, tularaemia, impetigo, ecthyma, cutaneous diphtheria, milker's nodules, and the peculiar granulomatous lesions which sometimes follow injuries in swimming pools, is discussed. Differentiation depends mainly on clinical and bacteriological exclusion of these various conditions.

Benjamin Schwartz

218. **Management of the Common Varieties of Scalp Ringworm**

J. M. BEARE. *British Medical Journal* [*Brit. med. J.*] **1**, 356–359, Feb. 13, 1954. 11 refs.

It is pointed out in this paper from the Royal Victoria Hospital, Belfast, that the differential diagnosis of the various types of ringworm of the scalp is important because treatment depends upon accurate mycological diagnosis. The author describes four types: those which fluoresce under Wood's light and those which do not, subdividing these again into those due to fungi affecting human beings and those mainly affecting animals.

The human type which fluoresces is caused by *Microsporum audouini*, and should always be treated by *x*-ray epilation of the scalp. It is emphasized that all contacts of the patient with this form of tinea capitis should be examined under Wood's light. The animal type which fluoresces is caused by *M. canis*, and should be treated by the local application of Whitfield's ointment. The time required for cure is variable, usually 6 to 8 weeks. The human type which does not fluoresce is caused by *Trichophyton sulphureum*, and is the most difficult to diagnose. Treatment is by *x*-ray epilation unless a kerion has formed, in which case it is unnecessary. The animal type which does not fluoresce is caused by *T. discoides*, the fungus of cattle ringworm. The lesion in these cases is usually a kerion which is self-healing. Loose hairs may be removed with forceps, and the acute inflammatory symptoms should be relieved; but the author does not consider that any form of treatment will shorten the duration of the infection.

E. Lipman Cohen

DERMATOSES

219. **Lupus Erythematosus and Polymorphous Light Eruptions. An Experimental Study on Their Possible Relationship**

M. M. CAHN, E. J. LEVY, B. SHAFFER, and H. BEERMAN. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **21**, 375–396, Dec., 1953. 8 figs., 37 refs.

During the month of June, 1952, 17 cases were seen at the Skin and Cancer Hospital of Philadelphia (University of Pennsylvania) in which the differential diagnosis between subacute lupus erythematosus and prurigo aestivalis could not be made with certainty either by clinical or histological examination. The 17 patients gave a definite history of altered sensitivity to sunlight, characterized by development of recurrent, transient erythematopapular eruptions—Hutchinson's so-called " summer prurigo ".

The methods of application of ultraviolet light and the clinical reaction obtained are described, together with the general pathological and local microscopic changes observed. From these studies, the authors conclude that lupus erythematosus is not a clear-cut concept, and that the reaction to light rays which occurred in these patients may in some cases represent a stage in the transition from latent to manifest clinical systemic lupus erythematosus.

G. B. Mitchell-Heggs

220. **The Treatment of Lupus Erythematosus with Chloroquine Sulphate**

G. HARVEY and T. COCHRANE. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **22**, 89–91, Feb., 1954. 1 fig., 1 ref.

Thirty cases of lupus erythromatosus were treated with chloroquine sulphate (" nivaquine "). The results obtained are as good as those from mepacrine hydrochloride (" atabrine "). The drug is much less toxic and so far has caused no dermal complications. The mode of action of chloroquine sulphate is unknown but future lines of investigation are suggested.—[Authors' summary.]

221. **Treatment of Pemphigus with Cortisone by Mouth**

A. H. CONRAD, J. GREENHOUSE, and R. S. WEISS. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph.* (*Chicago*)] **69**, 66–74, Jan., 1954. 1 ref.

The authors describe in some detail the effects of treatment with cortisone by mouth in 5 cases of pemphigus vulgaris, 2 of pemphigus erythematosus (Senear–Usher syndrome), and 1 of pemphigus foliaceus, giving the laboratory findings. Cortisone controlled or cleared the eruption in all cases except that of pemphigus foliaceus. Large doses (in one case 900 mg. a day) were given, and in one case of pemphigus vulgaris the cortisone was supplemented by heparin-sodium and later by nitrogen mustard. One patient, a man of 43, whose skin had cleared completely with a dose of 600 mg. of cortisone daily, later relapsed and died despite the resumption of treatment. ACTH (corticotrophin) produced no response in the 3 cases in which it was tried.

[Beyond the statement that " the patient must be followed indefinitely and supportive treatment with the drug given " no details of maintenance dosage are given.]

J. E. M. Wigley

222. **Pemphigus and Other Bullous Dermatoses: Correlation of Clinical and Pathologic Findings**

J. G. BRENNAN and H. MONTGOMERY. *Journal of Investigative Dermatology* [*J. invest. Derm.*] **21**, 349–363, Dec., 1953. 5 figs., 21 refs.

The authors have reviewed the records of 508 patients with serious bullous dermatoses seen at the Mayo Clinic since 1907, in whom the presence of various types of pemphigus was suspected. From the data so obtained pemphigus was diagnosed in 426 of the cases, the remaining 82 showing conditions not classified as true pemphigus. The histopathology and clinical appearances observed in these two groups of cases are described and compared. Although appearances in cases of one group may simu-

late those of the other group clinically, it is concluded that true pemphigus has definite histopathological features which render it distinct from the other forms of so-called pemphigus.

(In the discussion which followed the paper, emphasis was placed on the fact that pemphigus is a serious systemic disease and that the possibility that acantholysis can be regarded as pathognomonic of the condition merits further study.) *G. B. Mitchell-Heggs*

223. **The Atrophic Lichens.** (A propos des lichens atrophiques)
M. PRUNIERAS. *Annales de dermatologie et de syphiligraphie* [*Ann. Derm. Syph.* (*Paris*)] **81**, 46–61, Jan.–Feb., 1954. 4 figs., 23 refs.

From the Clinique de l'Antiquaille, Lyons, the author reports a case of lichen atrophicus in which early lesions showed a histological picture suggestive of lichen planus, while older lesions were more suggestive of scleroderma. The differential diagnosis from " white spot disease " is considered and the literature is reviewed. It is suggested that in classification lichen atrophicus should occupy a place between the main group of lichen planus and scleroderma along with the licheno-sclerodermic complexes described by Gougerot. *James Marshall*

TUMOURS

224. **The Reddish-Orange Fluorescence of Necrotic Cancerous Surfaces under the Wood Light**
F. RONCHESE, B. S. WALKER, and R. M. YOUNG. *Archives of Dermatology and Syphilology* [*Arch. Derm. Syph.* (*Chicago*)] **69**, 31–42, Jan., 1954. 8 figs., 12 refs.

Under Wood's light the necrotic surface of ulcerated squamous carcinomata is reported to show a vivid, orange-red, " burning-coal " fluorescence. The same fluorescence has been seen in cases of ulcerated carcinoma of the breast and in one case of facial fibrosarcoma, but a variety of other ulcers (including rodent ulcer) do not fluoresce, but appear uniformly deep violet in colour. Keratotic lesions on the other hand show a white fluorescence. The red fluorescence is entirely superficial and is only seen when necrosis is present. A streptomyces whose cultures fluoresced in the same way was isolated from one case.

A number of colour photographs are reproduced.
B. Lennox

225. ***para*-Aminobenzoic Acid Therapy in Lymphoblastoma Cutis and Mycosis Fungoides**
C. J. D. ZARAFONETIS, A. C. CURTIS, and L. W. KIRKMAN. *Cancer* [*Cancer* (*N.Y.*)] **7**, 190–201, Jan., 1954. 6 figs., 12 refs.

The use of *para*-aminobenzoic acid (PABA) in the treatment of lymphoblastoma cutis and mycosis fungoides was suggested by its beneficial effect in cases of myelogenous leukaemia treated at the University of Michigan Hospital, Ann Arbor, although this effect was considered to be less than that of other agents. Seven patients with lymphoblastoma cutis and 2 with mycosis fungoides received sodium or potassium *para*-aminobenzoate for periods up to 46 months. The initial dosage was usually 2 g. 2-hourly by mouth, but this was generally reduced later. Clinical and histological improvement resulted in all these cases, but relapse occurred in some when the treatment was stopped or when the dosage was inadequate. Once improvement had occurred and been maintained for some weeks, the treatment in most cases was discontinued, being resumed should the patient's condition relapse.

The most frequent side-effects of PABA were nausea and vomiting, which disappeared on stopping the drug, after which treatment could usually be resumed without further difficulty. Hypoglycaemic attacks may occur during PABA therapy, and are best prevented by instructing the patient to eat well while under treatment. Of the two salts used, potassium *para*-aminobenzoate is to be preferred, as with the sodium salt water retention may become troublesome. Evidence of potassium intoxication was not found, and was not to be expected from the dosage used. The mode of action of PABA in these conditions is unknown, but the drug appears to be a valuable addition to their treatment. *G. W. Csonka*

226. **ACTH and Cortisone in the Treatment of Keloids**
F. RONCHESE and A. B. KERN. *New England Journal of Medicine* [*New Engl. J. Med.*] **250**, 238–240, Feb. 11, 1954. 3 figs., 6 refs.

ACTH and cortisone were tried at Rhode Island Hospital, Providence, in the treatment of 5 cases of keloid formation. A female aged 17 had undergone bilateral mastoidectomy at the age of 4, after which keloids formed behind both ears. Radiotherapy was given and later the keloids were excised. When she was seen some years later a large keloid was observed on each of the original sites. She was given an intramuscular injection of 25 mg. of ACTH, the keloids were excised, and ACTH in a dose of 20 mg. was injected 6-hourly thereafter. The result was satisfactory, only a very small tumour reappearing behind the left ear. Keloids on the abdomen and knee were unaffected. A woman aged 28 had keloids on the chest on the site of old acne lesions; these recurred after excision and radiotherapy. She was given 25 mg. of cortisone by mouth three times a day for 3 weeks, and cortisone ointment containing 16·6 mg. per g. was applied for a month. She complained of pain and irritation in the scars; the keloids reformed, and during the following 3 months they increased in size and symptoms became more severe. In 2 cases keloids appeared where the lobes of the ears had been pierced. In one of these patients, a girl aged 14, they were excised and cortisone ointment was applied for 2 months, but the keloids reformed. In the fifth case in the series a keloid appeared at the site of an injury to the neck of a girl aged 11. It was excised and cortisone ointment applied, but the growth recurred.

The authors conclude that surgery with radiotherapy remains the treatment of choice in this condition.
E. Lipman Cohen

Paediatrics

INFANT FEEDING

227. **A Study of the Comparative Response of Young Infants to Human Milk and to Various Types of Cow's Milk Formulas**

M. A. HATFIELD, R. A. SIMPSON, and R. L. JACKSON. *Journal of Pediatrics* [*J. Pediat.*] **44**, 32–45, Jan., 1954. 4 figs., 11 refs.

From the State University of Iowa comes this report of a study carried out at the Obstetrical School nursery of 180 normal, full-term, newborn infants who were fed from birth for 6 days on either breast milk, adjusted fresh cow's milk, or one of 4 different milk formulae prepared from frozen or heat-sterilized, canned, evaporated milk. The milk mixtures (of which the composition is given) each supplied about 20 Cal. per ounce (0·7 cal. per ml.) and were comparable in regard to content of protein, fat, and carbohydrate. The study was carried out to ascertain if heat-treated milk mixtures, because of the supposed destruction of amino-acids or the formation of toxic or irritant substances during their preparation, would affect the nutrition or gastrointestinal tract of infants fed on them. Approximately equal numbers of infants of equal sex distribution were allocated to each of the 6 groups, and they were carefully observed for the 6 days of the test, the weight, number, size, colour, and consistency of the stools being recorded daily; special features such as red buttocks were also noted.

All the infants were vigorous and had made satisfactory progress by the end of the 6 days; none had diarrhoea, and there was no meconium staining of the stools after the 3rd day. From the information thus collected the only positive findings were that the breast-fed infants had stools which were more liquid and greener than the others, but on the other hand tended to have less irritation of the buttocks. They also appeared to have a greater initial weight loss and a slower gain in weight at the end of the 6-day observation period.

[Although 33 infants aged 1 to 8 weeks were also studied as out-patients and were fed on the same milk mixtures used in the nursery investigation, no breast-fed infants were included in this series for comparison.]

David Morris

228. **Clinical and Chemical Studies in Human Lactation**

F. E. HYTTEN. *British Medical Journal* [*Brit. med. J.*] **1**, 175–182 and 249–255, Jan. 23 and 30, 1954. 14 figs., 35 refs.

In a series of studies of human lactation carried out at Aberdeen Maternity Hospital the author first sought the most efficient method of obtaining 24-hour samples of milk, the aim being to empty the breast completely without disturbing normal milk production. By comparing the volume of milk obtained over 24 hours by skilled hand expression (from 83 subjects) or (from 85 subjects) with a mechanical breast pump, the "humalactor" (Ratcliff, *Brit. med. J.*, 1951, **2**, 234), in each case with the milk yield in the previous 24 hours as estimated from test weighing of the infant, it was shown that the yield obtained with the humalactor was, on the average, nearer to the figure expected than that obtained manually. Moreover, the humalactor method requires less time and is more comfortable to the patient.

Using the humalactor, the author then obtained 31 series of consecutive 12-ml. samples, taken throughout the period of emptying, from 20 subjects. On analysis of these it was found that a rise in fat content always occurred at the end of the feed owing, it is suggested, to "adsorption of the fat globules to the large secretory and duct surface of the breast", a similar rise in fat content being found when a rubber sponge was soaked in breast milk and emptied by compression. The lactose content on the other hand fell throughout the feed, probably as a result of the changing fat content, a rise in the proportion of fat in milk causing the proportion of water to fall by displacement and the milk therefore holding less of its water-soluble constituents. Changes in the total nitrogen content were variable, as might be expected, casein being partly adsorbed to the fat and varying in concentration with the fat content, and the concentration of soluble protein varying with the proportion of water.

Analysis of 49 24-hour samples collected by humalactor at the usual feeding times from 42 subjects showed that the yield of milk at 6 a.m. (the last previous feed having been at 10 p.m.) was significantly greater, and that at 10 p.m. significantly smaller, than that obtained at other times, which remained more or less constant. Although the fat content varied considerably through the day, especially in the first week of lactation, it was always at a minimum at 6 a.m. and at a maximum at 10 a.m., whereas the lactose and total nitrogen content showed no systematic change throughout the day.

The author then studied the 24-hour volume and composition of 240 samples of milk from 194 subjects at various stages of lactation, but chiefly in the early weeks. The volume was found to rise rapidly during the first week and then more slowly. The lactose content rose rapidly during the first week from a low initial level, then more slowly until it reached a stable value of about 6·9 g. per 100 ml. during the first month. On the other hand the total nitrogen content and the protein content fell rapidly but smoothly during the first 3 days and then more gradually to reach a level of about 1·0 g. per 100 ml. in the second month. The fat content was low during the first few days, increasing gradually to reach a maximum by the second month. This level varied from individual to individual, but it was generally possible by the seventh day to estimate fairly accurately what the ultimate value would be.

Finally, the differences in yield and composition of the milk on the seventh day of lactation in 150 subjects, 121

of whom were primiparae, were studied. Both the yield and the composition varied over a wide range, but there was no significant difference between the mean values for primiparae and multiparae. The fat content was the most variable, and there was evidence to show that it did not even remain constant in the same individual in different lactations. *Elaine M. Osborne*

NEONATAL DISORDERS

229. **The Prognosis of Infants Resuscitated after Neonatal Asphyxia.** (L'avenir des nouveau-nés ranimés)
G. TARDIEU and J. TRÉLAT. *Revue neurologique* [*Rev. neurol.* (*Paris*)] **89**, 259–265, 1953. 3 figs., 14 refs.

The authors report the results of a study of 138 children who were known to have suffered from asphyxia at birth. The subjects were divided into three groups according to the period of apnoea, and were examined for signs of mental deficiency, cerebral palsy, motor disturbances, and severe behaviour disorders. Gesell's test was employed [but most regrettably the age at which these children were tested is not stated].

From their results [which are presented in a far from clear manner] the authors conclude that severe asphyxia at birth is attended by serious neurological consequences in many instances, and that the degree of injury is positively correlated with the period of asphyxia. *M. MacGregor*

230. **Blood Sugar Levels in Babies Born of Diabetic Mothers**
G. M. KOMROWER. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **29**, 28–33, Feb., 1954. 4 figs., 17 refs.

In a study carried out at St. Mary's Hospitals, Manchester, the author set out to assess what constitutes hypoglycaemia in infants born of diabetic mothers and to determine its effect on mortality among these infants. Observations were made on 21 normal full-term infants and 40 infants born of diabetic mothers; the majority of the latter group were delivered by Caesarean section in the 37th or 38th week of pregnancy. To 25 of the 40 "diabetic" babies 50% glucose was given at fixed intervals during the first 8 hours of life, a total of 2 g. being given in all. The remainder were not given glucose and feeding was begun only when the infants cried from hunger. Blood sugar estimations were made first on cord blood and then on peripheral blood from the heel at half an hour, and 1, 2, 4, 12, and 24 hours after birth. Details of the methods used are given.

The results for the normal infants showed a wide scatter at any one time, but the bulk of the results lay around the mean. Comparison of the values showed that whereas most normal infants soon attained a reasonably stable blood sugar level, the values in the "diabetic" babies usually stabilized slowly at a rather lower level, showing a rapid fall in the first few hours of life with a slow rise towards the end of the first 24 hours. No significant difference was found in the blood sugar levels of the 25 babies given glucose during the first 8 hours of life and of the 15 not so treated. The author believes that the routine administration of glucose to these infants is not necessary. In many cases in this group the blood sugar level was below 35 mg. per 100 ml., but only 4 infants showed symptoms suggestive of hypoglycaemia, from which the author concludes that infants accommodate well to sudden reductions and low levels of blood sugar. There were 7 deaths among the infants of diabetic mothers, but in each case there was an obvious cause of death, and hypoglycaemia was not considered to be a contributory factor. *B. S. P. Gurney*

231. **Studies on the Renal Concentrating and Diluting Mechanisms in the Premature Infant**
P. L. CALCAGNO, M. I. RUBIN, and D. H. WEINTRAUB. *Journal of Clinical Investigation* [*J. clin. Invest.*] **33**, 91–96, Jan., 1954. 4 figs., 19 refs.

At the Children's Hospital, Buffalo, the authors gave a 25% solution of mannitol by intravenous infusion to 4 premature infants aged 5 to 23 days who had been kept without either milk or water for 12 to 18 hours previously. Urine was collected under oil and blood samples were drawn before, during, and after the infusion and the osmotic pressure and electrolyte content of these fluids were determined. Similar determinations were carried out on 12 other premature infants who were prepared in the same way but were not given mannitol. During the infusion the urine flow increased greatly, but its osmolar concentration fell. One of the 4 infants was given vasopressin intravenously during the mannitol loading; this produced no increase in reabsorption of water or concentration of urine, suggesting that the lower concentrating capacity of premature infants is of tubular (end-organ) origin. Sodium and chloride excretion were greatly increased during the infusion, but the excretion of potassium was only slightly increased. There was a variable rise in glomerular filtration rate and a rise in the creatinine:inulin ratio during mannitol loading. The same premature infants were shown to dilute their urine to values comparable to those in adults during the diuresis following a single water load.

[Whether the subjection of these infants to extensive, painful, and potentially harmful investigations to obtain information which could hardly benefit them in any way was ethically justifiable is a matter on which the abstracter has grave doubts.] *J. Lorber*

232. **Studies of the Mechanical Fragility of Erythrocytes. II. Relation to Physiologic Jaundice of the Newborn Infant**
D. YI-YUNG HSIA, R. B. GOLDBLOOM, and S. S. GELLIS. *Pediatics* [*Pediatrics*] **13**, 24–29, Jan., 1954. 3 figs., 42 refs.

In this paper from Beth Israel Hospital, Boston, the authors seek to show that the excess of bilirubin in the blood of newborn infants is related to an increased mechanical fragility of the erythrocytes, which is greatest at birth and falls to normal levels by the 5th or 6th day, the serum bilirubin level rising during the same period. In a series of infants whose blood was examined during the first 24 hours of life a direct correlation was demonstrated between erythrocyte fragility at that time and

the subsequent degree of bilirubinaemia attained. It is considered that these findings support the theory that the blood at birth contains a proportion of abnormal erythrocytes, mainly macrocytes, which break down and disappear during the neonatal period, the excess of bilirubin thus formed, together with functional immaturity of the liver, accounting for the physiological jaundice of the newborn. *M. Baber*

233. **The Effect of Ingestion of Plasma Thrombin on the Coagulation Time in the Newborn Premature Infant.** (Action de l'ingestion de thrombine plasmatique sur le temps de coagulation chez le nouveau-né prématuré)
H. PIGEAUD, H. GABRIEL, —. BARBAUD, and T. CHANDELIER. *Presse médicale* [*Presse méd.*] **62**, 225–226, Feb. 13, 1954. 4 figs., 3 refs.

Using a method which necessitates collecting only one drop of blood on a glass slide, the authors found that the mean coagulation time in 5 premature newborn infants rose progressively during the first 5 days of life from 3·11 to 5·27 minutes. In another group of 9 premature infants given an adequate dose of plasma thrombin by mouth each day, the coagulation time fell steadily over the same period from 5·16 to 3·23 minutes.

[It is perhaps fortunate for the authors' graphs that the mean coagulation time on the day of birth was 5·16 minutes in the treated group and 3·11 minutes in the control group.] *P. C. Reynell*

CLINICAL PAEDIATRICS

234. **Use of Unsaturated Fatty Acids in the Eczemas of Childhood**
J. H. S. PETTIT. *British Medical Journal* [*Brit. med. J.*] **1**, 79–81, Jan. 9, 1954. 22 refs.

Previous and conflicting reports by other workers regarding the results of treatment of eczema in patients of all ages with unsaturated fatty acids, given orally and applied locally, are discussed. As the basis of the claims made seemed to the author unsatisfactory, he undertook the present investigation, in which the unsaturated fatty acids, linoleic and linolenic acids, were given either in capsules or in an ointment.

Of a series of 27 patients with infantile and atopic eczema, ranging in age from 18 months to 15 years, 15 were given a daily application of an ointment composed of 1·7% of linoleic acid and 0·8% of linolenic acid in a hydrous base, and also daily by mouth one capsule containing 0·27 g. of linoleic acid and 0·13 g. of linolenic acid in arachis oil; the other 12 children, who acted as controls, were given the routine hospital treatment. The investigator did not know which cases were receiving the special treatment. The results showed no evidence that the treatment by local application and oral administration of unsaturated fatty acids was a satisfactory substitute for the usual treatment.

In a further investigation, 20 young patients with infantile and atopic eczema were given one capsule containing linoleic and linolenic acid daily for approximately 4 months in addition to the routine hospital treatment. From this investigation also the author concluded that unsaturated fatty acids have no value as an adjunct to the usual treatment of infantile or atopic eczema. *B. S. P. Gurney*

235. **Acrodynia Associated with Excessive Intake of Mercury**
J. G. DATHAN. *British Medical Journal* [*Brit. med. J.*] **1**, 247–249, Jan. 30, 1954. 10 refs.

The literature on the association of mercury and acrodynia is reviewed and 13 cases of acrodynia seen in the children's ward of a Stoke-on-Trent hospital over a period of 15 months are reported. In all the cases one particular brand of teething powder had been given over varying but considerable periods. Two of the cases, which are described in detail, were fatal, bronchopneumonia complicating the acrodynia. One of the children had been given 64 powders, the other only 12, but a considerable amount of mercury was found in the urine and in tissue specimens from liver, kidney, and brain in both cases. The first child was thought to have received an overdose of the powders, while the second was probably hypersensitive to the calomel they contained.

Holding the view that mercurial poisoning is the cause of acrodynia, the author tried dimercaprol in the treatment of this condition with good results. He advocates the inclusion of calomel in Schedule I of the Poisons List. *Elaine M. Osborne*

236. **Tumors Arising within the Spinal Canal in Children**
A. T. ROSS and O. T. BAILEY. *Neurology* [*Neurology*] **3**, 922–930, Dec., 1953. 3 figs., 9 refs.

Sixty-three tumors of the spinal cord and its coverings were found in a survey embracing material from a teaching medical center, a city hospital, and a large private hospital. Thirteen of the 63 tumors (20%) occurred in children under 16 years.

Of the 13 spinal cord tumors in children, 7 were intramedullary and 6 extramedullary. Clinically, the intramedullary tumors were usually characterized by painless symmetrical involvement of the spinal cord, whereas the extramedullary tumors usually began with radicular pain and unilateral signs. Examination of the cerebrospinal fluid could not be relied upon as a feature differentiating the two groups. However, the elevation of cerebrospinal fluid protein was of considerable diagnostic value in suggesting the presence of a spinal cord tumor since it was elevated in all but one.

The importance of searching for spinal cord tumor in progressive neural dysfunction in childhood is illustrated by the fact that in only 2 of the 13 proved instances was this diagnosis entertained originally. On three occasions the admission diagnosis was post-poliomyelitic syndrome. In this group the possibility of a spinal cord tumor should be considered early to prevent irreversible destruction of nervous tissue and unnecessary orthopedic procedures.

The prognosis depends upon the accessibility of the tumor, the histologic type, and the time of operation. Eight of the 13 patients are living but all except 2 have some residual neurologic deficit.—[Authors' summary.]

237. **Developmental Dysarthria**
M. MORLEY, D. COURT, and H. MILLER. *British Medical Journal* [*Brit. med. J.*] **1**, 8–10, Jan. 2, 1954. 2 refs.

The authors reserve the term "developmental dysarthria" for dysarthria which is not associated with neuromuscular disorders elsewhere, as in spastic diplegia. Boys are affected twice as often as girls, and in 10 out of 18 cases examined at the Royal Victoria Infirmary, Newcastle upon Tyne, there was a family history of a speech defect. Birth injuries, prematurity, and emotional disturbances do not appear to be responsible. In two-thirds of the authors' cases voluntary movements of the tongue, lips, or palate were manifestly spastic, but in the remaining one-third the abnormality of movement occurred only during speech, and these cases the authors regard as examples of "articulatory dyspraxia". Although the intelligence of the 18 children studied was within the range of normal, in half of them there had been some delay in the development of language. The speech in cases of developmental dysarthria is slow, clumsy, and often explosive, and the response to treatment is usually slow. This is in marked contrast with cases of dyslalia, a term reserved by the authors for instances of temporary consonant substitution, in which language develops at the normal time, speech is fluent if unintelligible, and the response to treatment is rapid.

J. Foley

238 (*a*). **Diagnosis and Treatment of Galactosaemia**
F. P. HUDSON, J. T. IRELAND, B. G. OCKENDEN, and R. H. WHITE-JONES. *British Medical Journal* [*Brit. med. J.*] **1**, 242–245, Jan. 30, 1954. 4 figs., 10 refs.

238 (*b*). **Galactose Diabetes**
E. G. FOX, W. M. FYFE, and A. W. MOLLISON. *British Medical Journal* [*Brit. med. J.*] **1**, 245–247, Jan. 30, 1954. 4 refs.

Both these papers are concerned with a rare inborn error of metabolism, the characteristic feature of which is the inability of the patient to complete the conversion of lactose to glycogen; lactose is converted to galactose in the normal way, but this substance cannot be further transformed to glycogen in the liver. In consequence there is an elevation of the blood galactose content and excretion of galactose in the urine. Sooner or later marasmus is an inevitable complication, together with enlargement of the liver, leading in untreated cases to hepatic cirrhosis. The earliest signs of the condition appear in the neonatal period; the infant fails to thrive, and other associated changes are jaundice, albuminuria, nuclear cataract, and eventually mental retardation. Anorexia is usually present but is variable, and the albuminuria and galactosuria may also be intermittent. Several theories have been advanced to explain the development of portal cirrhosis, but none has gained general acceptance. In some of the recorded cases there was a gross amino-aciduria but in others urinary excretion of amino-acids was normal. Occasionally the disease is familial.

For diagnostic purposes it is necessary to establish that the reducing substance present in the urine is galactose, and available chemical tests and chromatography are reliable for this purpose. Liver function tests may be abnormal. The essential step in treatment is the removal of lactose from the diet. If this is done in the early stage the manifestations of the disease are largely reversible, but if diagnosis is delayed the prognosis is poor.

In the first of these papers Hudson and his colleagues at the University of Liverpool describe 4 cases, the clue to the diagnosis in the first case being the finding of a sugar content of 222 mg. per 100 ml. in the cerebrospinal fluid when the child was 3 months old. The fasting blood sugar level was 190 mg. per 100 ml., the glucose tolerance curve abnormal, rising to 285 mg. after one hour, but the urine showed a normal amino-acid content. In this case response to a lactose-free diet was very satisfactory, but their other 3 cases terminated fatally and diagnosis was not established during life. In all 3 cases a diffuse hepatic cirrhosis was found at necropsy.

In the one case described in the second paper by Fox and colleagues from Stobhill General Hospital, Glasgow, an unusual feature was remittent pyrexia of undetermined origin, a finding which has been mentioned in some previously reported cases. This boy was admitted to hospital at the age of 4 months because of failure to thrive, when the liver was found to be enlarged three finger-breadths below the costal margin. Repeated examination of the urine showed no abnormality until the 35th day after admission, when a trace of albumin was detected; on the 46th day Benedict's test became positive, and the reducing substance was proved to be galactose. At no time was there any gross amino-aciduria. The patient improved when given a lactose-free diet and began to put on weight, but there was no reduction in the size of the liver. He suddenly collapsed and died about 5 months after admission to hospital. At necropsy the liver was regularly enlarged, and showed a diffuse monolobular cirrhosis. No glycogen was present in the sections of liver examined.

Jas. M. Smellie

239. **Atonic–Hypertonic Dysphagia in Infancy.** (Die atonisch-hypertonische Dysphagie des Säuglings)
K. NITSCH. *Monatsschrift für Kinderheilkunde* [*Mschr. Kinderheilk.*] **102**, 1–4, Jan., 1954. 5 figs.

The author reports a series of cases of persistent vomiting in children during the first few weeks or months of life which were investigated at the Cecilienstift Children's Hospital, Hanover. After excluding pyloric stenosis, infection, feeding errors, obstruction, and other possible causes he decided that the condition resembled that described by Catel in 1937 as "atonic–hypertonic dysphagia", the typical radiological picture of which was found in 23 cases, an incidence of 4·8% of all children presenting at the hospital with vomiting and 22% of all children with persistent vomiting. He describes 5 cases briefly, of which the first was that of a child of 8 weeks who had begun to vomit a few days after birth. There was no clinical or radiological evidence of pyloric stenosis, but there was up to 5 hours' delay in emptying of the stomach, which varied greatly in size and shape during this time, waves of peristalsis

being at times relatively frequent and at others absent. A similar alternation occurred also in the oesophagus, an atonic phase being followed by a hypertonic phase, sometimes within a few seconds. In the second case, although the stomach tended to empty quickly, similar radiological appearances were found, the stomach outline showing broadening and atony which would be absent a few seconds later, while the oesophagus would widen periodically as if some invisible instrument were being passed. In the third case there were similar appearances in the oesophagus and also signs of an oesophagitis associated with regurgitation of stomach contents. In all cases the radiological changes were strictly in accordance with the clinical findings—that is, on days free from vomiting no radiological changes could be demonstrated, and vice versa.

From the author's experience there appear to be two main types of case of atonic–hypertonic dysphagia: (1) that in younger infants, whose symptoms disappear relatively quickly, together with the abnormal radiological appearances; and (2) in older children (up to 9 months) in whom vomiting has been present intermittently since soon after birth, though it may vary greatly in frequency; they may even develop oesophagitis with haematemesis. The condition settles down in all cases with the introduction of thickened feeds, feeding in an upright posture, and sedatives.

The author has observed similar radiological appearances from time to time in older children, and suggests that some cases of " nervous " vomiting in such children may have a similar aetiology. In the main, however, the condition tends to disappear spontaneously before the age of 18 months. *J. G. Jamieson*

240. **Gastro-enteritis in Infancy in London**
I. TAYLOR. *Lancet* [*Lancet*] **1**, 202–203, Jan. 23, 1954. 1 fig.

The death rate from gastroenteritis in infancy in London fell from 23·8 per 1,000 in 1895 to 0·8 per 1,000 in 1951, this decline being particularly marked since 1945. The author, working in the Public Health Department of the London County Council, has investigated the possible causes of this reduction in mortality, which has been more marked in London than in the country as a whole, although other large cities have also shown a lower mortality over the same period. It is assumed, therefore, that the universal improvement in social conditions and public health control is not the basic cause but that other causes peculiar to London have also been at work. It is pointed out that as the birth rate has increased since 1945, there is actually a larger susceptible population.

There is evidence that improved treatment, in the form of chemotherapy, antibiotics, and correction of dehydration by intravenous infusion, has been in part responsible for the reduction in mortality. The author notes in this respect that intravenous therapy came into general use in the years 1943–4 and was followed by a reduced mortality in 1945. From a study of the admission records of cases of gastroenteritis at a London hospital in recent years the author concludes that the proportion of severely ill cases has declined. An attempt to assess the role of the increasing use of dried milks for infant feeding, as diminishing the sources of infection, was inconclusive. A study of the incidence of infantile gastroenteritis in different districts within London showed that a significant improvement in housing conditions has been accompanied by a fall in the death rate from this cause. In the London boroughs where the disease is notifiable there has been a marked fall in incidence since 1945. A milder form of epidemic dysentery is still prevalent, however, and the rate of spread of this infection does not suggest that there has been any very great improvement in hygiene.

The author concludes therefore that the causative micro-organism in gastroenteritis is less prevalent, and that this is probably the most important single factor in the reduction of mortality. *J. N. Harris-Jones*

241. **Some Observations on Umbilical Hernia in Infants**
G. E. WOODS. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **28**, 450–462, Dec., 1953. 11 figs., 38 refs.

Umbilical hernia developed in 106 infants under the age of 6 months out of a total of 573 seen at a Bristol Infant Welfare Clinic between 1948 and 1951. After discussing the embryology and anatomy of this condition in detail, the author analyses these cases and a further 177 seen in hospital practice. The condition is significantly commoner in twins, in premature infants, and in infants weighing more than 9 lb. (4 kg.) at birth. Other possible predisposing factors are breech delivery and unusual length of the umbilical cord. Coloured infants are more frequently affected than white. Mild umbilical sepsis plays a definite part in the aetiology of the condition, but more prolonged granulomatous inflammation of the stump seems to act as a preventive. In the author's experience complications are unknown, and in the majority of cases the hernia, even if it is large, will resolve spontaneously in the first few years of life. Strapping and the application of a truss interfere with spontaneous closure and are contraindicated. Operation is rarely found necessary in untreated cases and should never be performed in the early days. *T. A. A. Hunter*

242. **Anorectal Rings in Infancy: Incidence and Significance**
L. E. HARRIS, H. P. F. CORBIN, and J. R. HILL. *Pediatrics* [*Pediatrics*] **13**, 59–63, Jan., 1954. 2 figs., 10 refs.

A remnant of the ano-rectal membrane in ring form was found in 236 out of 1,716 consecutive infants born at St. Mary's Hospital, Rochester, Minnesota. In all the 1,716 cases rectal examination consisted in careful manual palpation with the tip of the fifth finger. The condition was four times more frequent in females than in males, but did not appear to cause symptoms. No treatment was given, and follow-up examination over a period of at least a year showed that the ring dilated spontaneously in all the infants. The authors state that a thick fibrous ring, which does not dilate spontaneously and which may cause symptoms requiring treatment, is found in some cases, but no such case was encountered in this large series. *M. Baber*

Medical Genetics

243. **Neurocutaneous Syndrome in the M Kindred. A Case of Simultaneous Occurrence of Tuberous Sclerosis and Neurofibromatosis**
W. J. SCHULL and F. W. CROWE. *Neurology* [*Neurology*] 3, 904–909, Dec., 1953. 4 figs., 17 refs.

A kindred is described in which 6 cases of classic tuberous sclerosis were distributed in a manner consistent with simple dominant inheritance. The coexistence of von Recklinghausen's neurofibromatosis and Bourneville–Pringle's tuberous sclerosis in one individual of this kindred is reported. It is suggested that mutation could readily account for such a finding.—[Authors' summary.]

244. **Genetic Aspects of Multiple Sclerosis**
R. MÜLLER. *Archives of Neurology and Psychiatry* [*Arch. Neurol. Psychiat.*] **70**, 733–740, Dec., 1953. 1 fig., 11 refs.

The incidence of disseminated sclerosis among the observed relatives of 750 patients with this disease was studied at the University Hospital of Uppsala, Sweden. A close relative of 27 (3·6%) of these patients was similarly affected. The incidence of the disease in the parents was $0{\cdot}3\pm0{\cdot}15\%$, in the sibs $1{\cdot}0\pm0{\cdot}21\%$, and in the children $2{\cdot}3\pm1{\cdot}15\%$. The incidence of parental consanguinity was $2{\cdot}2\pm0{\cdot}68\%$, which was no higher than that among the general rural population of Sweden. The author states that the incidence of disseminated sclerosis in the general population could not be determined with certainty, but was believed to be somewhat lower than in the relatives of the patients. The difference, however, was considered to be very small, and it is therefore concluded that genetic factors play a minor part in the aetiology of the disease. *Harry Harris*

245. **Familial Juvenile Disturbances of the Epiphyses of the Fingers and Toes.** (Familiäre juvenile Epiphysenstörung an Fingern und Zehen. Thiemannsche Krankheit)
W. SWOBODA. *Österreichische Zeitschrift für Kinderheilkunde und Kinderfürsorge* [*Öst. Z. Kinderheilk.*] **9**, 235–246, 1954. 7 figs., 11 refs.

246. **The Variability of Sickle-cell Rates in the Tribes of Kenya and the Southern Sudan**
H. FOY, A. KONDI, G. L. TIMMS, W. BRASS, and F. BUSHRA. *British Medical Journal* [*Brit. med. J.*] **1**, 294–297, Feb. 6, 1954. 12 refs.

A survey of the distribution of sickle cells in the blood in 44 tribes and sub-tribes in Kenya and 26 in the southern provinces of the Sudan is reported. In a few Kenya tribes the distribution of blood groups was also determined. The authors found considerable variation within the tribal groups, possible explanations of which are discussed, with particular mention of genetic drift. Despite this variability, they consider that some of their results may be of ethnological significance: for example the widely distributed Nilotes of Central Africa are divided according to sickling rates into two main groups, the Nilote tribes of the Sudan having very low rates and those of Kenya and Uganda medium or high rates, and these two groups differ also in their cultural background. *H. Lehmann*

247. **Dermatoglyphic Study of the Palms of Mongols and their Parents and Siblings.** (Étude dermatoglyphique des paumes des mongoliens et de leurs parents et germains)
R. TURPIN and J. LEJEUNE. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **29**, 3955–3967, Dec. 14, 1953. 13 figs., 10 refs.

A study was made at the Hôpital Saint-Louis, Paris, of the palm prints of 93 mongols, 246 first-degree relations of mongols (147 parents and 99 siblings), and 768 control subjects. The characters analysed were: (1) horizontal arrangement of the skin ridges in the distal part of the palm; (2) distal position of the axial triradius in the palm; (3) patterns on the hypothenar eminence directed towards the ulnar border of the palm; and (4) the transverse palmar crease.

A system of scoring for each of these characters enabled the authors to distinguish by means of the total score all but 5% of the mongols from the controls and all but 5% of the controls from the mongols, while the distribution of the total scores of the relations of the mongols showed a significant deviation from that of the controls in the direction of the mongols. [The scores for each type of relation are not given separately.] *C. O. Carter*

248. **Study of a Family Including Four Mongol Brothers and Sisters.** (Étude d'une famille comportant quatre frères et sœurs mongoliens)
R. TURPIN and J. LEJEUNE. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **29**, 3979–3984, Dec. 14, 1953. 5 figs., 6 refs.

In the family studied the eldest child (a boy) was probably a mongol and the second (a girl), third (a girl), fourth (a boy), and seventh (a boy) almost certainly mongols. The fifth child (a boy) and the sixth (a girl) were normal. Photographs of three of the mongol children are reproduced. The mother of these children was mentally normal, but her palm prints showed mongol characteristics and she had a fissured tongue, as also had her father and sister. The father of the mongol children had microphthalmia of one eye and this abnormality was also present in other members of his family. *C. O. Carter*

249. **Mongolism in Both of Monozygotic Twins**
R. J. YOUNG. *Archives of Disease in Childhood.* [*Arch. Dis. Childh.*] **29**, 55–59, Feb., 1954. 2 figs., 43 refs.

Public Health and Industrial Medicine

EPIDEMIOLOGY AND IMMUNIZATION

250. **A Silent Epidemic of Poliomyelitis**
H. H. MALHERBE. *South African Medical Journal* [*S. Afr. med. J.*] **28**, 68–71, Jan. 23, 1954. 6 refs.

Since January, 1953, at the Poliomyelitis Research Foundation Laboratories, Johannesburg, the virus of poliomyelitis has been successfully isolated by tissue culture directly from the stool. The technique employed is a modification of that introduced by Enders, Weller, and Robbins in 1949 (*Science*, **109**, 85; *Abstracts of World Medicine*, 1949, **6**, 490) for the propagation of poliomyelitis virus in culture of extraneural tissue. The author states that an antiserum produced against one of the three types of poliomyelitis virus is specific for that type and will not neutralize the other two; it is thus possible to identify the agent causing a cytopathogenic effect in tissue culture. In South Africa all three types of poliomyelitis virus were isolated during 1953, no type being found which was not neutralized by one of the known antisera. This laboratory work forms the basis of the present paper, which indicates the extent to which poliomyelitis may spread without producing recognizable signs or symptoms.

A child, aged 4 years, developed signs of respiratory distress, with vomiting and slight pyrexia. Progression was rapid, with palatal paralysis and cranial-nerve palsy, and the patient died 6 days later. On clinical grounds poliomyelitis with bulbar paralysis was diagnosed, although the child was not a known contact. The extent of infection among children at the nursery school attended by the patient was then investigated. Suspensions of stools were individually inoculated into tissue cultures. Specimens from 3 teachers and one student teacher were negative, but the percentage of positive stools from the children was high (60·9). It is believed that in Johannesburg there was a widespread infection with Type-3 virus, but that immunity was established in a large proportion of the children in the areas from which these cases came.

Discussing the spread of poliomyelitis virus, the author suggests that under certain circumstances and for a limited period during the disease salivary transmission may be important, especially in a nursery school, and that this route of infection may play as large a part as faecal transmission. "If faecal transmission is a significant factor . . . it would be reasonable to suppose that modern methods of sanitation tend to shield children from early contact with the virus, leading to a rise in the number of older non-immune persons." It is noteworthy that of 24 children whose stools were positive at the first examination 3 were still excreting the virus after 7 weeks. The author also suggests that as more rapid means of detecting the virus are evolved, it may become practicable to test the stools of patients and close contacts before releasing them from isolation, thus preventing them from spreading the virus. He considers that until a reliable vaccine is produced, early infection with the virus may offer the best protection against attack at a later age, when paralysis might be more severe.

A. Thelwall Jones

251. **The Current Epidemic of Rabies [in West Germany].** (Über den derzeitigen Tollwutseuchenzug)
G. SCHOOP. *Zeitschrift für Hygiene und Infektionskrankheiten* [*Z. Hyg. InfektKr.*] **138**, 415–426, 1954. 7 figs.

Since the end of 1950 a remarkable epidemic of rabies has been spreading through West Germany. The outbreak originated with the invasion of Poland in 1939, but during the following 2 years it appeared to have been almost extinguished. However, it then flared up again, particularly among wild and game animals, and for the last 10 years the disease has been spreading over an ever-widening area. Control of the epidemic has been difficult owing to the fact that the disease in its present form attacks especially foxes and (more rarely) badgers. In 20 experimentally infected foxes studied by the author the incubation period varied from 12 to 50 days. The foxes first showed changes in behaviour followed by a paralytic stage affecting the muscles of the eyes, lower jaw, and limbs. The duration of the disease varied between a few hours and 5 days. The diseased fox does not usually bite his own genus except during the rutting season, from February to April. Thus the maximum spread of the disease occurs in the early part of spring and the epidemic rages until the beginning of summer.

In spite of the rapid dissemination of rabies among wild animals the number of cases in man amounted only to 18 in Hesse in the first 5 months of 1953, but should the disease spread to domestic animals the danger of human infection would be very great. The accepted measures for the control of rabies have long been enforced by law in Germany, but no provision is made for the extermination of the infection among wild animals. It is suggested that the number of foxes and badgers should be drastically reduced by shooting in and out of season, or by treating their earths with hydrocyanic acid during the winter and until the middle of June.

Franz Heimann

252. **Characteristics of Spread of Infectious Hepatitis in Schools and Households in an Epidemic in a Rural Area**
V. KNIGHT, M. E. DRAKE, E. A. BELDEN, B. J. FRANKLIN, M. ROMER, and L. O. COPPLE. *American Journal of Hygiene* [*Amer. J. Hyg.*] **59**, 1–16, Jan., 1954. 4 figs., 4 refs.

In this description of an epidemic of 152 cases of infective hepatitis with jaundice, involving schoolchildren and their families in Cooper County, a rural area in the State of Missouri, in the first 6 months of

1951, the authors make an evaluation of the mode of spread of the infection in households and in the three schools concerned. They note that sanitary defects of structure and habit were no worse in the epidemic area than in the rest of the county. The number of cases became noticeable in January, 1951, and by the time the investigating team began work in April, 65 cases had been reported.

The chief symptoms were an upper respiratory tract infection followed, after a week, by anorexia and nausea, the passage of dark urine and pale stools, and the appearance of jaundice which lasted for a few days to 2 weeks; there were no deaths. In 37 out of 40 patients examined, the cephalin–cholesterol flocculation test was markedly abnormal. The cases were about equally divided between the sexes, and the majority occurred in school-children. Altogether, 78 families were involved, and a time-table of case incidence which showed two peaks at 26 and 55 days from the occurrence of the index case corresponds with the known incubation period of 25 to 30 days; the total case incidence was nearly 5%, as against 0·07% elsewhere in the county. A comparison of family secondary attack-rates with school attack-rates revealed a striking difference, the former being 2 to 8 times greater than the latter.

A search was made at the mid-point of the epidemic for non-icteric cases, and 10·4% of 134 children examined were found to have enlarged livers without jaundice. A small-scale study of the possible prophylactic value of gamma globulin midway through the epidemic was inconclusive as both the treated and control groups showed a very low incidence of jaundice during the period of observation. The authors conclude from the fact that 69% of index cases in families occurred in school-children that the schools performed the function of infecting new family groups, but that the homes were the areas of greatest risk of infection, and that personal contact was the mode of spread. *F. T. H. Wood*

253. **Results of a Trial of Vaccination against Influenza in the Winter of 1952–3.** (Resultaten van een proefvaccinatie tegen influenza in de winter 1952–1953)
J. D. Verlinde, O. Makstenieks, and C. A. G. Nass. *Nederlandsch tijdschrift voor geneeskunde* [*Ned. T. Geneesk.*] **98**, 559–565, Feb. 27, 1954. 1 fig., 7 refs.

In anticipation of an influenza epidemic in January and February, 1953, an experiment was devised by the authors at the Netherlands Institute for Preventive Medicine, Leiden, to test the efficacy of vaccination in groups totalling about 40,000 persons, half of whom were vaccinated between November 15 and December 15, 1952, with one of three vaccines: monovalent A^1 (70% FM_1, 30% Liverpool subtype), monovalent B (100% Lee), or polyvalent A^1B (35% FM_1, 15% Liverpool, 50% Bon type). The mild epidemic which materialized affected only about 10% of the general population, and the virus was found to differ from both FM_1 and Liverpool subtype of A^1 virus, while in England it was provisionally identified as Scandinavian subtype.

Comparison of the morbidity rates for the groups given the different vaccines and the controls revealed no statistically significant differences, except possibly between the composite polyvalent and monovalent A^1 vaccine group and the controls. Although the epidemic strain was not identical with either of the A^1 strains used in the vaccine, vaccination was followed by the development of antibodies to the epidemic strain. The results were considered to be inconclusive. *R. Crawford*

254. **The Hazard of Diphtheria in Adults**
J. T. Lewis. *Medical Officer* [*Med. Offr*] **91**, 17–20, Jan. 8, 1954.

From purely theoretical considerations the author attempts to determine the state of immunity to diphtheria in the general population which must be expected to result from the large-scale immunization of children, and discusses the consequent epidemiological risk among adults. On immunological grounds he distinguishes four categories with different grades of susceptibility to the disease: (1) the susceptible, consisting of non-immunized persons who have had no contact whatever with the diphtheria bacillus or its products; (2) the potentially susceptible, who have been immunized at some time in the past, but in whom the level of circulating antitoxin in the blood is now low (0·002 unit or less per ml.); (3) the potentially immune, with a blood antitoxin level of 0·002 to 0·02 unit per ml., who may give either a negative or a positive Schick reaction; and (4) the immune, with an antitoxin titre of more than 0·02 unit per ml., who may, in the author's opinion, be regarded as " immune to clinical diphtheria, no matter how heavy and severe the infecting dose of organisms may be ".

The author then goes on to argue that owing to the reduction in the carrier rate resulting from large-scale immunization, a high proportion of those immunized in childhood will receive no further stimulus or " latent immunization " after the initial " priming ", so that their blood antitoxin level will tend to fall with increasing age, and susceptibility will eventually be highest among the adult population. If there were a complete absence of carriers and if 80% of children underwent prophylactic immunization, the author calculates that approximately 75% of the adults in the population at some future date would be susceptible or potentially susceptible to diphtheria. From the few local carrier surveys carried out recently in Great Britain it would seem that the carrier rate throughout the country is more likely to be low than high, and it is suggested that 60 to 70% of adults may now be susceptible. However, the lesser risk of spread of infection among adults than among children makes a widespread epidemic unlikely even if a highly virulent organism were to be introduced. To enable epidemiologists to assess the position more accurately, however, an extension of carrier surveys " would be of very considerable value ", as would a knowledge of the antitoxin levels among blood donors, as representing a sample of the adult population.

[A leading article in the same issue of the journal points out that such an extension of the surveys would make it easier to prepare for an immunization campaign among adults should the necessity arise, and further that experience in outbreaks of diphtheria in Dundee and

Tyneside has shown it to be impossible to assume the existence of a state of absolute immunity on the basis of a high blood level of antitoxin. A state of high immunity is always relative and may be broken through by infection with large numbers of organisms of high virulence. During the last decade the tendency of diphtheria to attack a greater proportion of adults in communities with a high immunization rate among children has repeatedly been observed, the best example being provided by the Copenhagen outbreak of 1943–45 (Ipsen, *U.N.R.R.A. Epidemiological Information Bulletin*, 1946, **2**, 369).] *K. S. Zinnemann*

255. **Investigation of an Outbreak of Bovine Tuberculosis in a Rural Area in Leicestershire**
R. W. KIND and M. C. BROUGH. *British Medical Journal* [*Brit. med. J.*] **1**, 372–374, Feb. 13, 1954. 7 refs.

An outbreak of tuberculosis in children who had been drinking milk from a tuberculous cow is described. Two children in a village in Leicestershire developed non-pulmonary tuberculosis during the same month, and both drank milk from the same farm. Inquiry of the sanitary officer for the county revealed that in the previous month a cow on this farm was found to be suffering from tuberculosis of the udder, tubercle bacilli being recovered from a routine sample of the milk. Other children who drank this milk were examined and 3 more were found to have tuberculous nodes in the neck which required treatment. In one of these cases the tonsils were removed, from which tubercle bacilli of the bovine type were cultured.

Tuberculin tests carried out among all the children in the area showed that there were more reactors among those who drank the infected milk than among those who did not. *Scott Thomson*

256. **Tuberculin–Histoplasmin Conversion Rates in Kansas City as an Indication of the Prevalence of Infection—Preliminary Report. I. Tuberculin Studies**
L. E. WOOD and H. L. MANTZ. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **69**, 227–233, Feb., 1954. 2 figs.

In view of the increasing cost and diminishing returns of mass radiological surveys the authors, on behalf of the Kansas City Tuberculosis Society and Health Department, have investigated the possibilities of tuberculosis control by means of the tuberculin test. Tuberculin and histoplasmin tests are performed annually on 2,900 to 3,900 children in kindergarten and infant schools in Kansas City. In addition, a special study has been in progress since 1949 in 7 schools, in which negative reactors are re-tested every 6 months for 4 years in order to determine the seasonal changes in infection rates, while all positive reactors are examined radiologically and their families are visited and urged to undergo similar investigation. In the various districts of Kansas City the tuberculin sensitivity rate among school-children during 1947–52 ranged from 1·2 to 3·1% and the annual death rate from tuberculosis during 1949–51 from 7·9 to 60·6 per 100,000, the latter being lowest in the districts in which the former was lowest and vice versa. The annual conversion rate to tuberculin, based on repeated tests, amounted to 0·8% in 1949 and 1950. The follow-up examination of 609 adult household contacts of 295 children with a positive reaction on first testing revealed 9 new active cases of tuberculosis in addition to 27 who were already known to have the disease; and among 328 child household contacts 3 children with active disease were found, in addition to 3 among the index cases. Among the 273 adults and 58 children who were "non-household" contacts of these 295 children, one new case and 23 known cases were found.

The authors are of the opinion that by the tuberculin testing of young children and the follow-up of contacts of positive reactors a higher yield of new active cases of tuberculosis can be obtained than by any other method. *Franz Heimann*

257. **Tuberculin–Histoplasmin Conversion Rates in Kansas City as an Indication of the Prevalence of Infection—Preliminary Report. II. Histoplasmin Studies**
M. L. FURCOLOW, M. J. WILLIS, L. E. WOOD, and H. L. MANTZ. *American Review of Tuberculosis* [*Amer. Rev. Tuberc.*] **69**, 234–240, Feb., 1954. 2 figs., 6 refs.

The histoplasmin sensitivity rate among about 13,000 kindergarten school-children tested in Kansas City during the years 1947–52 ranged from 5 to 24% in different districts. The histoplasmin conversion rate amounted to 2·98% per year during the first 6 years of life and 7·72% per year thereafter. The complement-fixation test for histoplasmosis gave a positive result in 12 out of 51 cases in which a positive histoplasmin reaction was found, the reaction in 18 cases being doubtful. Radiological examination revealed active lung lesions in 10 of the histoplasmin-positive cases and healing lesions in 7. It is concluded that the histoplasmin test in young school-children is a valuable means of diagnosis in areas where histoplasmosis is prevalent. *Franz Heimann*

INDUSTRIAL MEDICINE

258. **Industrial and Laboratory Evaluation of a Silicone Protective Cream**
R. R. SUSKIND. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **9**, 101–112, Feb., 1954. 4 refs.

This article describes the clinical and laboratory evaluation of a silicone–bentonite cream, with particular reference to its protective qualities when applied to the skin, the effects of repeated application, and its stability *in vitro*. The clinical effectiveness of the cream was observed in selected groups of workers at one manufacturing plant (A) for 8 months, and at another (B) for 2 months. At Plant A 114 persons exposed to substances potentially harmful to the skin used the cream. In each case details were recorded of previous skin trouble, present skin affections, previous use of protective creams, and all possible contactants encountered at work. Instruction in the proper method of application and removal of the cream was given. The skin of each

subject was examined monthly, and the individual's opinion on the cream was sought. Of the 44 who had eruptions before using the cream, 24 reported improvement, which was most marked in workers exposed to corrosion inhibitors in light turbine oil, degreasing solvents such as xylene and heavy naphtha when used intermittently, lubricating oils, and soluble and insoluble cutting oils. No benefit was noticed in skins exposed to kerosene or waterglass. At Plant B (where experiments are still in progress) improvement occurred in skin lesions among persons exposed to water-soluble coolants, insoluble cutting oils, metallic dusts, sulphuric acid fumes, and rust preventives. No improvement occurred in skins exposed to lacquer thinners, which dissolved the cream.

Observations on 114 subjects at Plant A indicated that the cream had a low toxicity as a skin irritant or sensitizer. The results of laboratory tests of the stability characteristics of films of the cream are described, and tended to confirm the clinical findings. *A. Lloyd Potter*

259. **Efficiency Studies of the Electrostatic Precipitator** K. E. LAUTERBACH, T. T. MERCER, A. D. HAYES, and P. E. MORROW. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **9**, 69–75, Jan., 1954. 2 figs., 6 refs.

In a study of the efficiency of the electrostatic precipitator, modified (*a*) to minimize air turbulence, and (*b*) to allow the connexion of a filter holder directly behind the unit, in the collection of airborne particles tests were carried out with an aerosol of sodium chloride solution labelled with radioactive sodium (^{24}Na); the method used is described in detail, with a diagram of the apparatus. The efficiency, as indicated by determinations of the radioactivity of the deposit collected by 3 molecular filters in series following the precipitator, was found to be extremely high. With an air flow of 8 to 23 litres per minute and with particle sizes of 0·2 to 0·7 μ, penetration averaged 0·02%, and was only 0·002% with particles of the largest mean size (0·7 μ).

M. A. Dobbin Crawford

260. **Polonium in Urine of Miners Exposed to Radon** M. SULTZER and J. B. HURSH. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **9**, 89–100, Feb., 1954. 1 fig., 13 refs.

In view of recent suggestions that the abnormally high incidence of cancer of the lung among uranium miners might be due to chronic exposure to radon "daughters" attached to dust particles, the authors have studied the excretion of the radon decay product polonium (^{210}Po) in urine as a possible rough indicator of such exposure. Radium C′, one of the alpha-emitting radon daughters, decays into radioactive lead (^{210}Pb), which is retained in the bones, and it is reasonable to suppose that miners exposed to radon and its daughters will accumulate a body burden of ^{210}Pb roughly indicative of the magnitude of their exposure; ^{210}Po is the "granddaughter" of ^{210}Pb and will be in equilibrium with the stored lead. The amount of the body polonium excreted in the urine is about double the amount of body lead, and it can be separated and estimated by means of an alpha-particle counter. Full details of the technique are given.

Samples of urine from 28 Utah uranium miners were analysed and concentrations of ^{210}Po varying from 2 to 38 $\mu\mu$c. per litre were detected, whereas in none of 14 samples from 7 students who had not been exposed to radon was any urinary polonium found. The authors therefore conclude that human subjects exposed to high radon levels do in fact accumulate a store of ^{210}Pb derived at least in part from radon daughters deposited in the lung. Further experiments are in progress to determine: (1) whether the original exposure to radon can be inferred from the measurement of urinary polonium, and (2) at what level of polonium excretion the probability of lung injury can be inferred. *A. Lloyd Potter*

261. **The Toxicity of Organic Salts of Lead.** (Toxicité de sels organiques de plomb)
P. VALADE and E. COSTE. *Archives des maladies professionnelles, de médecine du travail et de sécurité sociale* [*Arch. Mal. prof.*] **14**, 584–593, 1953. 6 figs.

In a study of the toxic effects of lead carried out by the authors at the Centre d'Études du Bouchet, Paris, eight groups of animals, each composed of one dog and 2 rabbits, were submitted to 20 periods of exposure for 30 minutes to the dusts of the organic lead salts, lead stearate and lead acetylsalicylate, over a period of 2 months. In the case of lead acetylsalicylate, 95% of the dust particles were under 1 μ in diameter, and the dust concentration was 333 mg. per cubic metre. All animals, but particularly the dogs, lost weight. There were no other clinical signs, and there was little evidence of anaemia. A large number of nucleated erythrocytes were found in the blood after the fifth exposure to dust, and punctate basophil leucocytes appeared after the eighth exposure.

Histological examination showed that both the lead salts produced identical pathological changes in the animals. The liver showed fatty changes, either confined to the peripheral periportal areas or spread diffusely. The Kupffer cells were increased in size and number, and it seemed likely that the observed changes were destined to result in cirrhosis. The renal lesions affected both glomeruli and tubules, the latter being more seriously damaged. There was infiltration of the renal parenchyma by leucocytes, and the general pathological picture was comparable to that of subacute nephritis due to lead poisoning. Pulmonary lesions consisted of nodules of thickening and infiltration of the interalveolar septa together with hypertrophy of the cells lining the alveoli; multinucleated giant cells were found in the more advanced lesions. The spleen showed infiltration of the pulp by reticulo-endothelial cells.

Histochemical studies designed to demonstrate the presence of lead showed that the reticulo-endothelial cells of the bone marrow, liver, and spleen contained the main deposits of the metal. Haematological examination of 68 workmen handling lead stearate and lead acetylsalicylate revealed that a number of these persons were anaemic, 45 showing a reduced erythrocyte count, in 6 cases to less than 4,000,000 per c.mm.

As a result of these observations the authors conclude: (1) that exposure to the dusts of lead stearate and lead acetylsalicylate causes haematological changes characterized by anaemia and the appearance of nucleated erythrocytes in the early stages of exposure; and (2) that the animal experiments suggest the possibility of the development of hepatic cirrhosis and subacute nephritis in persons exposed to these lead salts. Moreover, the lead which is stored in the reticulo-endothelial system may be released into circulation at a later date.

W. K. S. Moore

262. **Early Effects of Lead on Lymphoid Cells**

D. O. SHIELS. *Medical Journal of Australia* [*Med. J. Aust.*] **1**, 30–33, Jan. 9, 1954. 1 fig., 5 refs.

Contrary to the opinion expressed by Lane (*Brit. J. industr. Med.*, 1949, **6**, 125; *Abstracts of World Medicine*, 1950, **7**, 226), who doubted if changes in the ratio of large lymphocytes and monocytes to small lymphocytes were sufficiently constant to be of practical value in the detection of early lead poisoning, the author has, by examination of a further 2,300 blood films, confirmed his own previous finding (Shiels, *Med. J. Aust.*, 1950, **2**, 205; *Abstracts of World Medicine*, 1951, **9**, 245) that there is a constant early response of the lymphocytes to lead absorption.

In the further study now reported from the Department of Health, Victoria, Australia, he gives details of the technique, with various modifications, used to examine 5 persons at the beginning and end of their first week of exposure to lead. The results again showed an increase in the ratio of the large lymphocytes to the small lymphocytes and in that of the large lymphocytes plus monocytes to the small lymphocytes, after exposure to lead. The author therefore still believes that this finding is of definite value in the early diagnosis of lead poisoning.

H. Payling Wright

263. **Comparative Exchange of Calcium, Lead, and Radioactive Lead in Dogs**

J. A. CALHOUN, R. MCLEAN, J. C. HUDSON, and J. C. AUB. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **9**, 9–22, Jan., 1954. 3 figs., 14 refs.

This paper records a metabolic study, carried out at Harvard University, of the localization, migration, and excretion of lead labelled with radium D (^{210}Pb) administered to 10 dogs by intravenous injection. Full details are given of the preparation of the materials used, of the technique of administration, of the metabolic routine and diet of the animals, and of the preparation of the biological materials for chemical analysis. ^{210}Pb was found to be toxic owing to its radioactivity even in the very small dosage of $0{\cdot}2 \times 10^{-1}$ mc. per kg. body weight. Excretion was mainly (67%) by the kidneys, and was unaffected by the administration of parathyroid extract, by giving a low-calcium diet, or by giving a diet rich in calcium. Possible reasons for the ineffectiveness of parathyroid extract are discussed. There was clinical evidence of kidney damage attributable to radioactivity in several of the dogs, and in 3 of them tubular swelling was found. In 5 there was a terminal azotaemia.

The lead excretion in those animals which survived for some months amounted to 60 to 80% of the quantity injected. On the 50th day after the last injection the daily excretion amounted to 0·4% of the residual lead. The remaining lead was stored almost entirely in the bones, very little being present in the liver, in other organs, and in the blood.

M. A. Dobbin Crawford

264. **Toxicity of Silica. II. Characteristics of Protein Films Adsorbed by Quartz**

L. D. SCHEEL, B. SMITH, J. VAN RIPER, and E. FLEISHER. *Archives of Industrial Hygiene and Occupational Medicine* [*Arch. industr. Hyg.*] **9**, 29–36, Jan., 1954. 2 figs., 7 refs.

Experiments were carried out at the Trudeau Foundation, Trudeau, New York, with the sera of immunized rabbits to determine the factors concerned in the adsorption of proteins by quartz particles and the properties of the resultant protein films. Quartz particles 1 to 3 μ in diameter were used, and the proteins studied were egg albumen, bovine albumin, and fibrinogen. A suspension of quartz particles in saline was added to a solution of protein in saline and the suspension maintained by gentle agitation for 12 to 18 hours. The suspension was then centrifuged, the supernatant fluid decanted, and the protein-coated particles washed in saline.

It was shown that adsorption of crystalline egg albumen is greatest when the *p*H is on the acid side of the iso-electric point, and decreases rapidly with increasing alkalinity. Adsorption was complete in about 4 hours, the protein concentration determining the amount adsorbed at any *p*H value; the deduction follows that the amount of protein adsorbed from tissue fluids by quartz particles would be increased by an increase in acidity of the fluid, such as occurs, for example, during an inflammatory response.

When quartz particles coated with egg albumen at *p*H 6·8 were suspended in serum from rabbits immunized against native and heat-denatured egg albumen it was found that the antigenic specificity of the adsorbed protein was lost and it reacted equally well with both types of antibody. It is therefore concluded that in the adsorbed state the egg albumen has an altered molecular structure. It was further found that the injection into rabbits of the albumen-coated particles caused the production of a heterogeneous antibody reacting with both native and heat-denatured egg albumen, and that this antigenic serum would also cause the agglutination of quartz particles coated with rabbit serum. Moreover, the serum of a rabbit immunized against such serum-coated quartz particles would cause the agglutination of particles coated with serum, with egg albumen, and with heat-denatured egg albumen. These agglutination reactions were not obtained in response to the injection of serum-coated particles of alpha-aluminium hydroxide, silica gel, olivine, beryllium oxide, opal, or quartz treated with aluminium hydroxide, which apparently prevents the alteration of the molecule of crystalline egg albumen on adsorption.

It is suggested that the toxic action of quartz particles may be the result of a foreign-protein reaction in the tissues.

M. A. Dobbin Crawford

Forensic Medicine and Toxicology

265. **Boric Acid Poisoning. Report of Four Cases and a Review of 109 Cases from the World Literature**
R. B. GOLDBLOOM and A. GOLDBLOOM. *Journal of Pediatrics* [*J. Pediat.*] **43**, 631–643, Dec., 1953. 47 refs.

Four cases of boric acid poisoning in infants, one of which was fatal, are here reported, all of which were the result of topical application of a boric acid preparation to the buttocks. The main clinical features were erythematous skin eruptions, followed by desquamation, diarrhoea, vomiting, and evidence of meningeal irritation. Boric acid was present in both urine and cerebrospinal fluid in all the cases.

Treatment was on general lines and directed against dehydration and infection. Post-mortem examination in the one fatal case revealed extensive haemorrhagic consolidation of the lungs, the cause of which could not be determined; there was no evidence of inflammation. Other findings were extensive subarachnoid haemorrhage, believed to be caused by birth trauma, left otitis media, and a confluent red skin eruption over the ears, chest, abdomen, and axillary regions with severe excoriation and oedema of the buttocks.

The authors conclude that the therapeutic use of boron compounds in any form should be abandoned.

P. N. Magee

266. **Transcutaneous Absorption of Boric Acid**
J. DUCEY and D. B. WILLIAMS. *Journal of Pediatrics* [*J. Pediat.*] **43**, 644–651, Dec., 1953. 8 figs., 25 refs.

The authors describe 3 cases (one fatal) of transcutaneous absorption of boric acid following topical application of this compound in powder form for napkin rash. The clinical features included erythema and excoriation of the skin in varying degrees of severity, vomiting, diarrhoea, dehydration, and evidence of meningeal irritation. The blood contained boric acid in a concentration of 1·88 to 5 mg. per 100 ml. and the urine 3 to 28 mg. per 100 ml.; the cerebrospinal fluid in the fatal case contained 5 mg. per 100 ml. Post-mortem findings included atelectasis of the left lung; cerebral, hepatic, and renal congestion; vacuolar and granular degeneration of the convoluted tubules; and vacuolation of the pancreatic acini. Analysis of the organs revealed a boric acid content per 100 g. of wet tissue as follows: kidney, 21 mg.; liver, 10 mg.; brain, 1·2 mg.; and muscles, 1·1 mg.

Treatment, which was general and supportive, included intravenous administration of fluids and whole blood to guard against dehydration and circulatory collapse, a high fluid intake with mercurial diuretics to assist excretion of boric acid, and prophylactic administration of penicillin and streptomycin.

The authors draw attention to the danger of applying boric acid powder to damaged skin, with the consequent risk of cumulative absorption, and to the need for considering the possibility of boric acid poisoning in all cases of diarrhoea and vomiting in infants. They consider that the practice of using dusting powder containing boric acid should be discontinued.

P. N. Magee

267. **The Use of Correctives in the Prevention of Barbiturate Intoxication**
T. KOPPANYI and J. F. FAZEKAS. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **226**, 597–606, Dec., 1953. 20 refs.

A "corrective"—now an almost obsolete term—is redefined as a substance protecting the patient against the undesirable side-effects or overdosage of a particular drug without interfering with the intended therapeutic effect of that drug. In the prevention of acute barbiturate poisoning three theoretically possible methods could be applied:

(1) By interference with absorption from the gastrointestinal tract by means of agents that produce vomiting or diarrhoea, or by increasing the rate of destruction of the barbiturate in the lumen of the tract. The combination of barbiturates with magnesium sulphate or sodium phosphate was tested experimentally but produced copious diarrhoea. Incorporation of the barbiturate in a non-digestible substance such as chicle (which would have to be chewed) has been suggested, but has not been tested and may prove to be impracticable.

(2) Employment of antagonists to enhance the elimination or metabolism of absorbed barbiturates. So far no suitable drugs of this type have been discovered.

(3) The most hopeful approach seems to be the incorporation with barbiturate drugs of physiological antidotes which either stimulate at the same sites at which barbiturates depress or act as competitive biological antagonists for identical enzyme centres. Experimentally, the authors showed by simultaneous intraperitoneal injections into mice of a central stimulant and a fatal dose of pentobarbitone sodium that only picrotoxin and pentylenetetrazol were protective, and that substances such as caffeine, strychnine, nikethamide, amphetamine, and "dexedrine" failed to offer significant protection. The drawback to picrotoxin, however, as a suitable corrective is its delayed onset of action. As pentylenetetrazol, on the other hand, is absorbed at the same rate and has the same time of onset of action as the intermediate and short-acting barbiturates, and does not interfere with their sedative or hypnotic effects, it seems to be the corrective of choice. Various combinations of pentylenetetrazol with barbiturates were administered to human subjects daily for one year without the development of untoward effects or increased liability to addiction. These tests showed that pentylenetetrazol in combination with phenobarbitone sodium in a ratio of 3:2, and with pentobarbitone or secobarbitone sodium in a ratio of 3:1 was the most suitable preparation for routine clinical use.

I. Ansell

Anaesthetics

268. **The Use of Arfonad in Controlled Hypotension**
C. J. KILDUFF. *Lancet* [*Lancet*] **1**, 337–338, Feb. 13, 1954. 1 fig., 9 refs.

" Arfonad " was used to produce hypotension in 50 patients undergoing operation on the head, neck, or chest wall at Queen Victoria Hospital, East Grinstead. In all cases general anaesthesia was induced with thiopentone and maintained with nitrous oxide and oxygen, supplemented with pethidine or more thiopentone. An endotracheal tube was inserted after relaxation with gallamine, and the patient allowed to breathe spontaneously. Blood pressure was recorded before and after the table was tilted 20 to 30 degrees in the reverse Trendelenburg position.

At first arfonad was given by continuous intravenous infusion, but this method was abandoned because technical difficulties could not be surmounted, repeated single injections being substituted. With the latter method the average total dose required was less than a quarter of that needed with continuous intravenous infusion. Dosage depended on age and on the response to tilting, the aim being to produce a blood pressure of 60 to 80 mm. Hg. For young patients, in whom the decrease on tilting was slight, the initial dose was 50 mg.; in older patients it was 10 to 30 mg. Subsequent doses were given at 10- to 15-minute intervals, and ranged from 10 to 30 mg. In all patients a satisfactory fall in blood pressure was obtained, but the field of operation was less dry than with the methonium compounds, while the postural sensitivity was greater. *Ronald Woolmer*

269. **Controlled Hypotension with Arfonad**
C. F. SCURR and J. B. WYMAN. *Lancet* [*Lancet*] **1**, 338–340, Feb. 13, 1954. 10 refs.

Controlled hypotension was produced with " arfonad " in 250 patients undergoing various operations at the Westminister Hospital, London. Administration was by intravenous drip infusion at the rate of 60 drops (equal to a dosage of 3 to 4 mg.) a minute. A substantial fall in blood pressure was produced in every case, but the dose required to maintain this varied widely; in a few cases it proved impossible to reduce the pressure below 60 to 80 mm. Hg. The hypotension could be rapidly reversed by administration of a vasopressor drug. The infusion was stopped a few minutes before the end of the operation, and by the time the operation was finished the blood pressure had usually risen to 100 mm. Hg.

The authors state that it was possible to obtain the required degree of hypotension in a much greater proportion of cases than with the methonium compounds, but the dryness of the field was not always commensurate with the hypotension. They prefer arfonad to the methonium compounds because its effects are more readily controlled and prolonged postoperative hypotension is rare. The use of arfonad does not, however, remove the dangers of hypotension, and perfect oxygenation must be assured throughout the period of anaesthesia. *Ronald Woolmer*

270. **The Concentration of " Pontocaine " Hydrochloride in the Cerebrospinal Fluid during Spinal Anesthesia, and the Influence of " Epinephrine " in Prolonging the Sensory Anesthetic Effect**
J. G. CONVERSE, C. M. LANDMESSER, and M. H. HARMEL. *Anesthesiology* [*Anesthesiology*] **15**, 1–10, Jan., 1954. 3 figs., 11 refs.

At the Albany Hospital, New York, the concentration of amethocaine (" pontocaine ") in the cerebrospinal fluid after its intrathecal injection in dextrose solution was estimated in 9 patients and in 6 who were given an injection of adrenaline as well. When adrenaline was added the concentration of amethocaine in the cerebrospinal fluid 5 minutes after injection was greater than it was when amethocaine alone was given. After 90 minutes, however, the amethocaine concentration was approximately the same in both groups. In the patients who did not receive adrenaline no sensory anaesthesia remained after 120 minutes, when the average amethocaine concentration was 0·8 mg. per 100 ml.; in those receiving adrenaline sensory anaesthesia persisted to the level of the fifth thoracic segment, even when the average amethocaine concentration had fallen to 0·25 mg. per 100 ml. The authors therefore question whether a " critical level " of local analgesic agent in the cerebrospinal fluid is necessary for the continuation of sensory anaesthesia. *A. M. Hutton*

271. **Studies with Transtracheal Artificial Respiration**
J. P. REED, J. P. KEMPH, W. HAMELBERG, F. A. HITCHCOCK, and J. JACOBY. *Anesthesiology* [*Anesthesiology*] **15**, 28–41, Jan., 1954. 6 figs., 15 refs.

The physiological effect of transtracheal artificial respiration was investigated experimentally at the Ohio State University Hospital, Columbus. Dogs which had been rendered apnoeic by injection of pentobarbitone sodium were insufflated with oxygen through a 13-gauge needle inserted into the trachea for a period of 30 minutes. The rate of oxygen flow was 15 litres a minute. There was no movement of the chest, excess oxygen escaping through the mouth and nose, but arterial carbon dioxide tension rose to very high levels. After this period a tapered steel cannula with an inside diameter of 0·14 inch (0·36 cm.) was inserted into the trachea and intermittent insufflation of compressed air (with chest expansion) was begun. The blood chemistry returned to normal, the artificial respiration being adequate.

The authors suggest that since this tapered cannula can be inserted quickly and with little difficulty it might be used for emergency resuscitation instead of a surgical tracheotomy. *A. M. Hutton*

Radiology

RADIOTHERAPY

272. **Changes in Sternal Marrow following Roentgen-ray Therapy to the Spleen in Chronic Granulocytic Leukemia**

W. B. PARSONS, C. H. WATKINS, G. L. PEASE, and D. S. CHILDS. *Cancer* [*Cancer (N.Y.)*] **7**, 179–189, Jan., 1954. 7 figs., 46 refs.

The mode of action of irradiation in the treatment of chronic granulocytic leukaemia has been the subject of several conflicting reports. In this study of the changes in the sternal marrow following radiotherapy, carried out at the Mayo Clinic, differential cell counts were made on smears obtained by aspiration biopsy of the sternal marrow of 12 patients just before and after courses of radiotherapy, the interval between the two counts ranging from 2½ to 13 days. *X* rays were applied over the spleen in 3 to 12 daily doses, and in no case was the sternum irradiated, the effects on the marrow being therefore indirect.

The chief change observed was a decrease in cellularity, due to a fairly uniform reduction in all cells of the granulocytic series with a tendency to a relative increase in mature neutrophils. The changes were on the whole, however, too variable to permit of a definite conclusion as to whether there was any acceleration of cell maturation or any effect of radiation on the erythropoietic system.

The authors conclude that examination of the sternal marrow provides more information than is given by the peripheral blood picture about the progress of a case and the response to treatment, but is not necessarily indicated as a routine procedure in every case, except when peripheral blood counts provide no sure indication of the status of the haematopoietic tissue. In general, further radiotherapy would be indicated for a patient in whom cellularity of the marrow remained high.

J. Walter

273. **Pathological Study of Retinoblastoma Treated by Radon Seeds and Radium Disks**

H. B. STALLARD. *Bulletin of the New York Academy of Medicine* [*Bull. N.Y. Acad. Med.*] **30**, 132–151, Feb., 1954. 11 figs.

The author describes his experiences at Moorfields Eye Hospital and St. Bartholomew's Hospital, London, in the treatment of 36 patients (37 eyes) with retinoblastomata by careful local irradiation. From 1934 to 1948 he used implanted radon seeds, but since 1948 has used radium disks consisting of a hollow platinum disk containing asbestos paper impregnated with radium salt or radioactive cobalt (^{60}Co). The disk, 5 to 15 mm. in diameter, is curved to fit the sclera exactly so as to deliver an even irradiation to the underlying tumour, the inner radius of curvature being 11 mm., the platinum wall thickness 0·5 mm., and the cavity depth 0·3 mm. The disk is held by a clip which is sutured to the sclera. Radium loading is calculated to give a dose of 3,500 r in one week at the apex of the tumour, this height being calculated as seven-tenths of the tumour diameter. The platinum case absorbs alpha and beta radiation so that only gamma rays reach the tissues.

Of the 36 patients treated, 28 have kept some useful vision in the treated eye, without recurrence of the tumour, and 10 of them have survived more than 5 years, 7 being still alive after 13 years, one after 6 years, and 2 after 5 years. Six others are alive without recurrence, but are blind. In the author's experience there is a reasonable hope of cure without loss of useful vision when not more than one-third of the retina is involved and the choroid is not infiltrated. Advanced cases are best treated by exenteration of the socket and postoperative irradiation. The use of Columbia-paste plaques holding radium needles and of teleradium and deep *x* rays (as employed by some surgeons) is not advised in the treatment of limited tumours as being more likely to be followed by blindness. Complications after such treatment have included cataract, retinal exudates and haemorrhages, and choroidal and sub-retinal haemorrhages.

In 8 eyes removed and examined in serial section after irradiation the tumour changes were extensive, involving particularly the cell nuclei and blood vessels. Complete disappearance of tumour cells, with fibrosis and calcification, was found in some cases. Retinal changes adjacent to the tumour included oedema, pigmentation, devascularization, and degeneration of the ganglion cells and rods and cones. Irradiation cataract was characterized by the appearance of "bladder cells" at the equator and posterior part of the cortex of the lens.

A. M. Jelliffe

274. **Radium Therapy of Carcinoma of the Lip.** (Die Radiumbehandlung des Lippenkarzinoms)

N. NICOLOV. *Strahlentherapie* [*Strahlentherapie*] **92**, 251–280, 1953. 4 figs., bibliography.

The author reviews a series of 253 cases of carcinoma of the lip treated between 1932 and 1945 by radiotherapy at the Lainz Municipal Hospital, Vienna. The importance of exposure to sunlight and of tobacco as predisposing factors is emphasized; there were significantly more smokers among patients with cancer of the lip than in a control series of cases of cancer of the skin, while the number of pipe-smokers equalled that of cigarette-smokers in the former compared with a heavy preponderance of cigarette-smokers in the control series. In males the lower lip was nearly 7 times more frequently involved than the upper, while in females the two lips were almost equally involved. Details are given of the clinical and histological types represented, and of the lymphatic routes of metastasis.

Treatment was with radium in all cases, though bulky projections were first reduced by superficial electrocoagulation. Surface moulds were used mostly, treatment being by protracted fractionation; the mould was worn 6 to 8 hours per day for a total of 50 to 60 hours, giving a surface dose of 5,000 to 6,000 r. Interstitial needles were used for lesions at the corner of the mouth or on the upper lip, and teleradium for the largest lesions. There was clinical evidence of involvement of lymph nodes (almost always submandibular or submental, rarely cervical) in 36 cases when first seen and in 8 later, in 7 of these within 3 to 6 months of treatment; secondary involvement of nodes was never found to develop in the first 2 months after treatment. If such nodes were mobile, even if bilateral, a Crile block dissection was carried out if possible, followed by treatment by surface mould or teleradium. Inoperable nodes received surface or teleradium treatment, and in rare cases were made operable thereby. Prophylactic surgery or irradiation was not used.

Recurrence of the primary growth occurred in 25 cases (10%) and was treated by radium needling, electrocoagulation, or both, with local healing in 23 cases. Over half the recurrences appeared within 3 to 6 months of treatment, and very few after a year. The prognosis is unfavourable if recurrence of the primary occurs within 6 months, and for recurrent metastases it is virtually hopeless, radium dosage being severely limited by previous treatment. No cases of late necrosis were seen, a fact which is attributed to the low intensity of the radiation.

Primary healing took place in 97% of cases. The absolute survival rates were 63·8% at 3 years and 52·5% at 5 years, the net survival rates being 86·5% and 83% respectively.

For infiltrating lesions the net survival rate was 74·2% at 5 years compared with 93·2% for superficial lesions. In cases with metastases the best results were obtained with surgery plus postoperative radiation. In general, the results of radium treatment for carcinoma of the lip are superior to those of surgery, especially when allowance is made for the relatively high proportion of unfavourable cases referred for radiotherapy, while the cosmetic results are unquestionably better.

J. Walter

275. **Cancer of the Tongue, Mouth, and Pharynx. Sex Differences in Prognosis following Radiotherapy**
M. H. Russell. *British Medical Journal* [*Brit. med. J.*] **1**, 430–434, Feb. 20, 1954. 2 figs., 2 refs.

The prognosis in relation to sex in cases of carcinoma of the tongue, mouth, and pharynx is discussed. The series included 673 cases of cancer of the tongue, 916 of cancer of the mouth, and 550 of cancer of the pharynx, all of which were treated by irradiation at the Christie Hospital and Holt Radium Institute, Manchester, between the years 1932 and 1942 inclusive. In addition, block dissection for involved cervical lymph nodes was carried out in some cases.

A review of the 10-year survival rate showed that the results were significantly better in females than in males. This difference was even more obvious in the "age-corrected" rate than in the crude survival rate. Further analysis showed that preoperative lymph-node invasion and postoperative recurrence, either locally or in previously unaffected cervical lymph nodes, occurred more frequently in males than females. The postoperative mortality rate was also lower in females. The various factors that may be responsible for these differences are discussed.

[It is not possible in an abstract to summarize the many detailed tables of results on which the author bases her conclusions.] *A. M. Jelliffe*

276. **The Influence of Various Factors on Metastases in Carcinoma of the Breast**
P. Rigby-Jones. *British Journal of Cancer* [*Brit. J. Cancer*] **7**, 431–437, Dec., 1953. 4 figs., 1 ref.

A review was made of all cases of carcinoma of the breast seen at the Royal Cancer Hospital, London, in the 10-year period 1937–47, totalling 1,626, with a view to assessing the influences of various factors on the appearance of the first recurrence. Of these, 679 patients developed recurrence following treatment which had removed all clinical evidence of disease, but only in 444 of these cases was there sufficient information for analysis. As 2 recurrences were detected simultaneously in 76 cases, 3 in 11, 4 in one, and 5 in another, the number of "first recurrences" in these 444 cases totalled 549, distributed among the following sites.

Bones	134
Skin	127
Lung and pleura	86
Regional lymph nodes	70
Lymph nodes opposite side	50
Liver	37
Brain and spinal cord	13
Mediastinal nodes	7
Abdominal, other than liver	6
Opposite breast	8
Original breast	5
Thyroid gland	2
Other lymph nodes	4
	549

A high proportion of recurrences in all sites occurred in the first 3 years, the number falling a little in the 4th and 5th years and being relatively small in the following years. There did not seem to be any definite relation between the time-interval and the proportion of local to distant metastases. The duration of life following the first recurrence depended upon the site, being short when the liver was involved and only slightly longer with metastases in the lungs and pleurae, whereas cases of skin recurrence had a much better prognosis and vertebral recurrences were also less rapidly fatal. The majority of patients died between 1 and 4 years after the recurrence appeared, but some survived for 5 and one for 8 years. The site of the first recorded recurrence bore little relation to the site of the primary tumour in the breast, although there seemed to be a higher incidence of metastases in the lung and pleura from tumours of the outer half, and in the liver from those of the upper half (contrary to accepted teaching). Similarly, the clinical

stage of the disease had little effect on the site of recurrence, adding weight to the opinion that prognosis is chiefly determined by the nature of the tumour.

The influence of postoperative *x*-ray therapy was shown by the development of metastases in the scar in 44% of untreated cases compared with 24% of those treated with *x* rays. Further, parasternal irradiation seemed to be of value in preventing parasternal recurrences when the primary tumour was in the inner half of the breast.

The results of this investigation support the opinion that the pattern of dissemination depends more on the nature of the primary tumour than on any other factor. It also suggests that, within the limits imposed by the character of the tumour, much can be done by treatment to assist in controlling the spread. *I. G. Williams*

RADIODIAGNOSIS

277. **Technique and the Dangers of Cerebral Angiography**

G. F. ROWBOTHAM, R. K. HAY, A. R. KIRBY, B. E. TOMLINSON, and M. E. BOUSFIELD. *Journal of Neurosurgery* [*J. Neurosurg.*] **10**, 602–607, Nov., 1953. 4 refs.

The authors discuss their experience at the General Hospital, Newcastle upon Tyne, of the complications of cerebral angiography, with particular reference to their causation and avoidance. They have carried out the procedure on 430 patients, the injection being unilateral in 334 cases and bilateral in 96; in 417 cases a percutaneous injection was made and in 13 cases the carotid vessels were exposed surgically before angiography was performed. There were 3 deaths, and complications occurred in 30 cases; the complications were transient in 18 cases, but in 12 they were severe and permanent.

The selection of cases to be subjected to the investigation is considered to be important for the avoidance of complications, cerebral angiography being particularly dangerous in cases of cerebral thrombosis and also carrying an increased risk in cases of head injury in the acute stage. While the incidence of complications could not be correlated with the use of any one of the three different dyes injected, the authors regard it as obvious that the weakest concentration of dye which will provide adequate visualization should be employed, and they show that the greater the number of injections made, the higher the incidence of complications. In 2 of the 3 fatal cases it was considered that the dye had produced an acute necrosis in small cortical blood vessels, and in the third case extensive thrombosis of the middle cerebral artery was found.

The possibility that the technique employed might be responsible for the sequelae is also discussed. Examination of the carotid vessels at necropsy revealed lesions of the intima on the posterior wall of the vessels punctured in all 3 fatal cases, with adherent thrombus in one case, these lacerations being a possible source of delayed cerebral emboli. Damage to cerebral capillaries resulting from the speed and force of the injection may also occur, and as a result of direct observations of the cortex made at operation they believe that it is possible to drive out blood from the cerebral capillaries for a sufficient period of time to cause severe ischaemia. On the basis of their experience suggestions are made for the avoidance of these complications. *J. E. A. O'Connell*

278. **Selective Segmental Bronchography with Water-soluble Contrast Media**

A. BERNSTEIN. *British Journal of Radiology* [*Brit. J. Radiol.*] **27**, 97–106, Feb., 1954. 14 figs., 9 refs.

The use of oily contrast media for bronchography, particularly if its elimination is incomplete is accompanied by certain dangers, such as the risk of pneumonitis or the formation of granulomata. The introduction of water-soluble contrast media has eliminated these dangers but has raised a new problem, namely, that because of the extremely irritating effect of these substances, the bronchographic procedure itself is more difficult and a much larger amount of local analgesic is required. Because of the risks of hypersensitivity or overdosage of the analgesic, therefore, the area of the bronchial tree examined should be as small as possible. In the author's view, reports of considerable damage being caused to the bronchial and alveolar walls by the water-soluble media have been much exaggerated.

In this paper he describes the technique used by him at the Queen Elizabeth Hospital, Montreal, in 25 cases. The lesion is located as accurately as possible by plain radiography and fluoroscopy. The special catheter devised and described by Métras (*Presse méd.*, 1944, **52**, 181) is introduced and the area to be examined anaesthetized with 1 to 2 ml. of 1 or 2% amethocaine. A small amount of contrast medium is then run in under fluoroscopic control and spot films taken immediately, one of these being in lateral and one in postero-anterior projection. Routine postero-anterior, lateral, and oblique survey films are also taken but are not regarded as essential.

The advantages of the spot-film technique are stressed; by it, films are made when contrast visualization is at its best and a record may be obtained of appearances which last for only a few moments. After the examination the patient is encouraged to expectorate. Follow-up radiography one hour later shows as a rule no residue and no contrast medium in the kidneys. When expectoration has been incomplete a general cloudiness may persist for up to 24 hours; this effect is caused by the carboxymethylcellulose base which is added to the water-soluble medium and eliminated more slowly than the iodine component. In all the author's cases penicillin was mixed with the medium. Five typical cases are described and illustrated.

John H. L. Conway-Hughes

279. **Cholangio-cholecystography.** (Cholangio-cholécystographie)

S. NEMOURS-AUGUSTE and N. BARAG. *Presse médicale* [*Presse méd.*] **62**, 300–304, Feb. 24, 1954. 15 figs., 5 refs.

The radiographic demonstration of the intra- and extra-hepatic biliary systems is determined by the functional integrity of the liver as shown by its ability to

extract the contrast medium from the circulating blood. In this paper the authors describe the results of 100 observations on 10 patients examined by cholangiocholecystography, that is, the exploration of the main and accessory biliary canals, following the intravenous injection of a new contrast medium, "*radiosélectan biliaire*". This method allows an appreciation of the different degrees of hepatic permeability to be made, since whenever there is a pathological weakness of the hepatic cell, the excretion of the contrast medium is slowed down.

Several eventualities can thus be observed. The biliary canals may not show up at all, the gall-bladder may show only after an excessive length of time, no part of the biliary system may be visualized, or the dye may be eliminated mainly through the kidneys and thus opacify the urinary bladder. Each of these possibilities is illustrated by clinical examples. Agreement between the results of cholangio-cystography and the laboratory and clinical findings was demonstrated in a number of cases. *A. Orley*

280. **The Place of Cholangiography by the Venous Route in the Radiological Investigation of the Biliary Tract.** (La cholangiographie par voie veineuse. Sa place dans l'exploration radiologique des voies biliaires)
J. Sénèque, R. Le Canuet, C. Debray, M. Roux, and J. Aussage. *Presse médicale* [*Presse méd.*] **62**, 281–285, Feb. 24, 1954. 13 figs., 18 refs.

In the authors' opinion the most important recent advance in the radiography of the biliary tract is the possibility of demonstrating the main biliary ducts directly without having to opacify the gall-bladder at the same time. This has been made feasible by the discovery of a contrast medium of low toxicity which, when injected intravenously, is eliminated rapidly and selectively through the liver in a concentration adequate for radiographic demonstration of the biliary ducts. When 40 ml. of this substance, N-adipin-di-(3-anilo)-2:4:6-triiodobisodium phenylcarbonate ("biligrafin"), is given intravenously it appears in the bile only a few minutes after injection. If the liver is diseased, the substance is rapidly eliminated through the kidneys in a concentration adequate for urography, but normally the liver excretes nearly 90% and the kidneys the remaining 10% of the medium. The authors recommend that the injection be given very slowly, drop by drop. Use of the medium is contraindicated in patients with iodine intolerance, as well as in those with diffuse parenchymatous lesions of the liver.

Radiographs are taken 15 minutes after the injection, and then every 15 minutes during the first hour and at half-hourly intervals thereafter, preferably with the patient in the erect position. The authors describe and illustrate in 13 reproductions of radiographs the appearances of normal and diseased biliary tracts, and of these tracts after removal of the gall-bladder by operation. The method is not intended to replace classic cholecystography, but is indicated only in cases of postoperative or congenital absence of the gall-bladder, or when the gall-bladder empties badly. *A. Orley*

281. **A New Method of Investigation of the Biliary Tract.** (Une nouvelle méthode d'exploration des voies biliaires)
R. Nadal and J. Vigneau. *Presse médicale* [*Presse méd.*] **62**, 293–294, Feb. 24, 1954. 6 figs.

The authors report their experiences over the last 6 months with a new German contrast medium, "biligrafin" (in France, "*radiosélectan biliaire*") [see Abstract 280]. This substance contains 64·32% of iodine, each molecule containing 6 atoms of the halogen. It is supplied in 20-ml. ampoules, each of which contains 4 g. of the salt, and the contents of 1 or 2 ampoules are given slowly, intravenously, over a period of 5 to 8 minutes.

The most suitable radiographic position was found to be the supine right oblique, although with obese patients the prone position proved more practicable. After the injection, radiographs were taken every 5 minutes for the first half hour, and then every quarter of an hour. These showed a rapid passage of the contrast medium through the liver, the intra- and extra-hepatic canals being the first to opacify, followed in about half an hour by the gall-bladder, the shadow attaining maximum density during the second hour.

The authors have found the new medium useful in cases in which, following cholecystectomy, the patient presents symptoms of inflammation of the biliary tract, and in cases of cholelithiasis, simple cholecystitis, internal biliary fistula, and primary biliary dyskinesia. The investigation is being continued. *A. Orley*

282. **Clinical Application of Portal Venography**
H. Fuld and D. T. Irwin. *British Medical Journal* [*Brit. med. J.*] **1**, 312–313, Feb. 6, 1954. 6 figs., 10 refs.

Percutaneous portal venography was first carried out on a human subject by Leger in 1951 (*Mém. Acad. Chir. (Paris)*, **77**, 712), and a number of reports on the subject have appeared since. The present authors describe their experience of portal venography in 50 cases at Sefton General Hospital, Liverpool.

The technique is not difficult if the spleen is enlarged. A lumbar-puncture needle with a short bevel is inserted just below the left tenth rib in the posterior axillary line or in the tenth intercostal space in the scapular line, a distinct resistance being felt when the spleen is entered. Good contrast is obtained with 50% diodone, 18 ml. being injected, and a single exposure is usually all that is required.

The method is useful in cases of splenomegaly of unknown origin and in the diagnosis of obstruction of the portal vein; it is also helpful in differentiating intrahepatic from extrahepatic venous block and in demonstrating the collateral circulation. By means of this method it is possible to decide whether a vascular anastomosis is likely to be of value, and the operation may be planned more accurately. *D. E. Fletcher*

283. **Functional Venography of the Lower Extremities**
H. B. Shumacker, T. C. Moore, and J. A. Campbell. *Surgery, Gynecology and Obstetrics* [*Surg. Gynec. Obstet.*] **98**, 257–272, March, 1954. 9 figs., 15 refs.

History of Medicine

284. **The Origin of Obstetric Nurseries**
S. H. CLIFFORD and W. C. DAVISON. *Journal of Pediatrics* [*J. Pediat.*] **44**, 205–212, Feb., 1954. 6 figs.

The practice of caring for newborn infants in separate nurseries seems to have been first introduced in the United States. The authors seek to trace the origin of the practice which, although of no great antiquity, is now largely forgotten.

The Johns Hopkins Hospital had obstetric nurseries, perhaps established by Whitridge Williams, by 1899, but the New York Lying-in Hospital seems to have kept the babies in cribs by the mothers' beds until 1902. The Boston Lying-in Hospital started by admitting chiefly unmarried mothers, but soon took the then courageous step of mixing the " respectable " with the " outcast " in the same wards. A separate night nursery was established at this hospital in the late 1890s, and it seems probable that it was the need for night nurseries that was the real origin of the separate obstetric nursery. In the first decade of the present century epidemics of diphtheria and scarlet fever gave impetus to their establishment, and the increasing affluence of patients generally permitted the trend to find full expression.

It is noted that the peak now seems to have been reached, and there is at present a growing tendency to return the babies to their mothers.

Calvin P. B. Wells

285. **History of Blood Transfusion**
N. S. R. MALUF. *Journal of the History of Medicine and Allied Sciences* [*J. Hist. Med.*] **9**, 59–107, Jan., 1954. 24 figs., bibliography.

The vital character of the blood was recognized in ancient times, and there are early references to its being drunk for the purpose of rejuvenation. There is no proof that it was ever given parenterally before the 17th century. The first detailed description of transfusion is given by Andreas Libavius (1615), but it does not appear that he ever carried out the procedure. In 1642 Georg von Wahrendorff is said to have injected wine and various medicaments into the veins of hunting dogs, and these may have been the earliest injections into the circulation. Francesco Folli of Florence claimed to have performed a transfusion in 1654, but there is no proof that he did more than describe a method. Johann Daniel Major (1664) wrote on intravenous medication and blood transfusion and suggested the use of an anticoagulant.

The first scientific experiments on blood transfusion were carried out by Wren, Wilkins, Lower, and other members of the newly formed Royal Society in the period 1665–7. Exsanguinated dogs were revived by direct and indirect transfusion; exchange transfusion was successfully performed, and there were many experiments on intravenous medication. Denis of Paris is credited with the first transfusion of blood into a human being, in June, 1667. He used the blood of sheep and calves. His fourth patient died—the first recorded transfusion reaction—and this mishap put an end to transfusion for over a century. Meanwhile, in November 1667, the Englishmen Lower and King successfully performed transfusion from sheep to man. Transfusion of sheep's blood was also carried out in Germany, and Elsholtz's *Clysmatica nova* (1667) contains the first illustration of an intravenous injection in man.

Transfusion was described but not practised in the 18th century; the period was very important, however, because it saw Priestley and Lavoisier's discovery of oxygen, the demonstration by Rosa that an animal in severe shock may be resuscitated by whole blood but not by serum, and Hewson's observations on anticoagulants. Bichat in 1805 carried out cross-circulation experiments which indicated definitely that oxygen is transported by the blood. Transfusion was reintroduced into England by James Blundell, the famous obstetrician, who appears to have been the first to use human blood for transfusion in man (1818). Prévost and Dumas (1821) discovered that blood can be made incoagulable by defibrination. By the end of the 19th century animal-to-man transfusion was finally abandoned and substantial progress had been made in the establishment of safe techniques. In the 20th century Karl Landsteiner's discovery (1900–1) of the existence of definite blood groups was of fundamental significance. The introduction of citrate by Hustin, Lewisohn, and Agote (1914–15)—some 23 years after its anticlotting action on the blood was first demonstrated—made direct transfusion almost obsolete and opened the way for the blood bank. Yudin of Moscow performed the first human transfusion with cadaver blood in 1930; transfusion with placental blood has not proved practicable.

W. J. Bishop

286. **The Ancestors of the *Presse Médicale*.** (Les ancêtres de la *Presse Médicale*)
R. VAULTIER. *Presse médicale* [*Presse méd.*] **61**, 1781–1785, Dec. 25, 1953. 10 figs.

This article provides a comprehensive survey of French medical periodicals from 1679, when Nicolas de Blegny first issued his *Nouvelles découvertes sur toutes les parties de la Médecine*, to the end of the 19th century, when *La Presse Médicale* appeared, and gives information concerning the editors and the type of subject matter to be found in each publication. The early journals, such as that of Blegny, emphasized novelty, sensation, and popular appeal. Under the influence of the scientific societies which flourished during the 18th century the number of more serious periodicals intended for the medical profession steadily increased, while during the 19th century the phenomenal growth in number of

general medical journals was accompanied by the foundation of many specialist journals.

The author gives full details of the format and quality of production of many of the medical periodicals mentioned, and shows how they have characteristics of their own that distinguish them from those in other sciences. In the publication of books the medical press has kept in step with improvements in materials and processes of illustration, but the high standards of precision required for medical work have meant that it has not been able to make full use of more recent developments in the printing and production of periodicals and magazines.

[The article, which is well illustrated, indicates clearly that early French periodicals contain a wealth of material of value to the student of medical history.]

F. M. Sutherland

287. **Plato's Concepts of Medicine**

L. S. KING. *Journal of the History of Medicine and Allied Sciences* [*J. Hist. Med.*] **9**, 38–48, Jan., 1954.

Plato regarded medicine as one of the two arts of the body—gymnastic, which is the maintenance of health by exercise and diet, and medicinal, which is the restoration of health by the use of drugs. As elsewhere in his teaching, reality is contrasted with appearance: thus, the aim of true medicine is to effect a cure; but just as false gymnastic art (cosmetics and adornment) gives only the appearance of health, so false medicine aims only at transitory improvement and has no regard to the true interest of the patient.

Every art has two aspects: the rational, based on the concept or " idea " and capable of exact measurement, and the empirical, based on conjecture and not susceptible of proof. Medicine is among the less exact arts, which include " husbandry, piloting, generalship, and music ", since it relies on inspired guessing as well as on accurate measurement. Plato's reality is the world of ideas, grasped by the intellect and not by the senses; medicine is a true art when based on scientific knowledge and a lesser art when merely empirical. Thus, the aim of modern medical science is to interpret phenomena in terms of general concepts or laws which have the validity of Plato's " ideas "; and for this purpose a particular case is of interest only in so far as it suggests a rule. Although the experimental method is modern, the basis for the distinction between medical practice and medical science and the concept of scientific method is found in Plato.

Plato's ideas on the ethics of medicine are, however, different from those held today. He discusses two aspects: the physician's obligations to his patient and his obligations to society. The true physician, skilled in his art and practising correctly, must consider only the good of his patient, the attainment of which is the object of his art. If he deviates from this purpose, particularly to make money, he is not a true physician. But though healing must not be sold only to those rich enough to buy it, neither must it, according to Plato, be given except to those who can be cured to live a normal and good life as part of the state. He supposes that Asclepius did not heal " bodies which disease had penetrated through and through . . . he did not want to lengthen out good-for-nothing lives. . . ." Thus medicine was not only a private relation between doctor and patient; the physician had also a responsibility to the state. The foundation for this ethic is in Plato's metaphysical concept of the good of the whole. The good of the whole—the state—includes the good of the part—the individual; thus what appears to be the good or health of the individual is specious: only the good of the state is real. This view is rejected by modern medical ethics; the individual has not yet been completely subordinated to the state and the physician is not required to be a judge.

W. J. Bishop

288. **An Unpublished Consultation Letter of Sir Thomas Browne**

M. MACKINNON. *Bulletin of the History of Medicine* [*Bull. Hist. Med.*] **27**, 503–511, Nov.–Dec., 1953.

The author presents the Latin text and English translation of a recently discovered letter written by Sir Thomas Browne to one of his colleagues, Dr. Samuel Bave of Bath. In May, 1642, Browne, then settled in Norwich after practising in Halifax, sent an old friend and patient, Sir Charles Le Gros, to Bath for treatment, communicating to Bave some of the facts of Sir Charles's case. He suffered from a " scorbutic miasma " associated with swelling which disfigured not only his legs with ulcers and spots, but the entire surface of his body with an impetigo of some sort accompanied by very troublesome itching. For this malady Browne had prescribed various remedies, including cathartics, diuretics, local applications, and numerous " anti-scorbutics " most of which are to be found in the *Pharmacopoeia Londinensis*, 1618.

Bave continued these measures and tried others as well, but Sir Charles was apparently a difficult patient who, although he faithfully took the baths and drank the potions prescribed, was averse to exercise, stayed indoors reading all day and half the night, and " destroys himself with sadness ". Despite the earnest solicitude of Browne and Bave, he made no permanent recovery. At his death Browne lost one of his oldest and closest friends, to whom he paid tribute when he dedicated his *Hydriotaphia* to Sir Charles's son, Thomas Le Gros.

H. P. Tait

289. **A Note on the Spanish Version of Dioscorides' *Materia Medica***

V. PESET. *Journal of the History of Medicine and Allied Sciences* [*J. Hist. Med.*] **9**, 49–58, Jan., 1954. 5 figs.

290. **Medical Aspects of the Assassination of Abraham Lincoln**

H. R. GILMORE. *Proceedings of the Royal Society of Medicine* [*Proc. roy. Soc. Med.*] **47**, 103–108, Feb., 1954. 18 refs.

291. **Some New Letters of Horace Wells Concerning an Historic Partnership**

H. K. BEECHER and C. FORD. *Journal of the History of Medicine and Allied Sciences* [*J. Hist. Med.*] **9**, 9–20, Jan., 1954. 1 fig.